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SYMPTOMATIC NEONATAL HYPOGLYCEMIA ASSOCIATED WITH TOXEMIA OF PREGNANCY

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DURING the first hours after birth, fasting normal newborn infants develop blood sugar levels which are considerably lower than those of fasting older children or adults.[1, 2] In premature infants[3] and in the offspring of diabetic mothers,[4-7] this hypoglycemia is even more marked. Yet it is so unusual in the newborn to find clinical signs clearly attributable to hypoglycemia that these low levels are often referred to as physiologic.[8] This report describes 8 cases of spontaneous hypoglycemia with symptoms beginning on the second or third day of life in infants born to mothers with toxemia. They differ from previously reported cases[9-12] by their self-limited course.

PATIENT MATERIAL AND METHODS

Of the 5 patients observed by the authors, 4 (B. M., D. B., P. B.,† and F. Z.) were born at The Johns Hopkins Hospital[1] and one (G. A.) at Baltimore City Hospital.[2]* The histories of two additional patients (R. F.[3]† and B. D.) were obtained from the Harriet Lane medical records and of another (R. T.) from the records of the Baltimore City Hospital.

Many of the blood sugar determinations are reported as total reducing substance (TRS). The others represent true blood sugar and were determined by the method of Somogyi-Nelson.[13] The chemical determinations on the patients at the Baltimore City Hospital were performed in the Pediatric Chemistry Laboratory, those at Johns Hopkins in the central hospital laboratory.

Tolerance tests were done on the first 3 infants (B. M., D. B., and P. B.). Glucagon‡ (30 meg. per kilogram) was given intravenously and capillary blood sugar determinations obtained at half-hour intervals for 2 hours. Epinephrine (0.03 ml. per kilogram of epinephrine hydrochloride 1:1,000) was given intramuscularly. Casein tolerance tests were done by

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†We wish to thank Dr. Henry Seidel for permission to report his private case P. B.

*We wish to thank Drs. Harold H. Harrison and Lawrence Finberg for permission to publish the cases from the Baltimore City Hospital.

†The case of R. F. has previously been reported by Dr. Lawson Wilkins.[3]

‡Glucagon was supplied by Dr. E. R. Kirtley of Eli Lilly and Company.

administering Casec (calcium caseinate), 1.5 Gm. per kilogram orally, and following the capillary sugar levels before and one-fourth, one-half, 1 and 2 hours after ingestion. Leucine (0.15 Gm. per kilogram) was given orally to one infant (D. B.) and blood sugar determinations followed for 2 hours.

CASE REPORTS

The first 2 cases are described in detail and their course illustrated in Figs. 1 and 2. The pertinent data on all of the infants have been summarized in Tables I and II. The remaining 6 case reports are in the appendix.

CASE 1.—B.M. (HLH No. B-43258) (Fig. 1), a 2,580 gram white male infant, was born on Aug. 5, 1957, 24 days prior to the expected date of confinement. His mother was 20 years old, Rh positive, para 0010, with a negative serologic test for syphilis, and in good health. At 34 weeks' gestation, she was hospitalized because of a 34 pound weight gain, blood pressure of 138/94, edema of the hands, and 1 plus albuminuria. On restricted activity and a low salt regime, a weight loss of 6 pounds occurred in one week. Labor began spontaneously 2 days later. The blood pressure during labor remained 130/94. Demerol and scopolamine were given 3 hours prior to delivery. Labor was uneventful, lasting $10^{24}/_{60}$ hours (the second stage was $^{50}/_{60}$ hours). The infant was delivered by the vertex in occipitoanterior position, with elective low forceps over a median episiotomy under nitrous oxide and oxygen anesthesia. The mother required repair of a fourth-degree laceration. The postpartum course was uneventful and her blood pressure was 104/70 on discharge.

The placenta weighed 380 grams and had an adherent clot over $^1/_3$ of the maternal surface.

The infant breathed at birth, cried in 40 seconds, and was described as in fair condition. Slight pallor and cyanosis were noted. Physical examination at 45 minutes of age was unremarkable. At 12 hours of life, routine glucose feedings were offered and taken well, as were the subsequent evaporated milk with 5 per cent carbohydrate feedings.

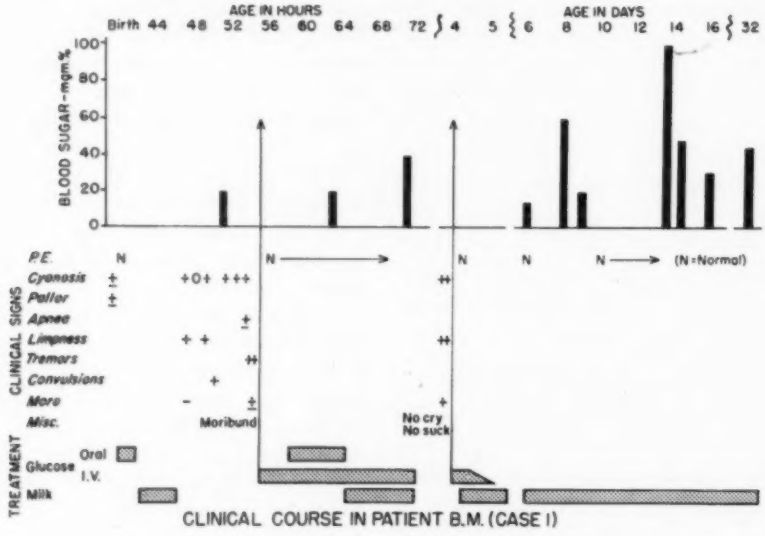


Fig. 1.

At 47 hours of age, the infant was observed to be limp, flaccid, cyanotic, and without Moro reflex. While he was being examined, the cyanosis gradually diminished. A glucose water feeding was attempted. Limpness and cyanosis increased and sucking reflex was absent. Jaundice was noted. The liver was palpable 1 cm. below the costal margin and the fontanel was tense. Bilateral subdural and ventricular taps were negative. During a venipuncture, the infant made jerking movements of all extremities. Blood chemistry determinations revealed the blood sugar to be 20 mg. per cent (TRS), nonprotein nitrogen 51 mg. per cent, calcium 9.3 mg. per cent, and bilirubin 16 mg. per cent. The blood type was O, Rh positive, direct Coombs test negative. The infant improved in color and tone. However, at 55 hours of age he again became cyanotic, hypopneic, jittery, and appeared moribund. Twenty cubic centimeters of 10 per cent glucose was given rapidly intravenously, followed by 55 c.c. by intravenous drip. The baby responded rapidly within a few minutes, lost all traces of cyanosis, and became less jittery. A lumbar puncture was performed at 63 hours of age with the glucose infusion running. The cerebrospinal fluid sugar was 45 mg. per cent. A blood sugar determination obtained at about 64 hours of age with 10 per cent glucose running intravenously at the rate of 10 c.c. per hour was 20 mg. per cent (TRS).

On the fourth day of life, the intravenous glucose infusion was temporarily discontinued. After 6 hours, the baby became quite flaccid, acrocyanotic, did not cry or suck, and the Moro reflex was poor. Twenty minutes after the glucose infusion was restarted, the infant looked better and began to take feedings. The bilirubin was 14.0 mg. per cent and the blood sugar 40 mg. per cent (TRS) with the infusion running.

On the fifth day, the infant was weaned from the infusion and maintained on frequent small feedings of evaporated milk 2:3 with water and 10 per cent added carbohydrate.

On day 6, after a 9 hour fast, the blood sugar was 14 mg. per cent with no apparent clinical signs of hypoglycemia. An intravenous glucose tolerance test was performed with 25 c.c. of 10 per cent glucose. The highest blood sugar was 64 mg. per cent at 1 hour. This had fallen to 40 mg. per cent at 2 hours, at which time 250 meg. of glucagon was given intravenously. In 30 minutes, the sugar was 50 mg. per cent, falling to 14 mg. per cent by the end of 2 hours. At no time during these procedures did the baby show any abnormal signs.

Thereafter, the baby did well on the frequent feedings. The blood sugar ranged around 60 mg. per cent (TRS) 2 to 3 hours after feedings.

On day 7, the nonprotein nitrogen was 60 mg. per cent, bilirubin 5.4 mg. per cent, phosphorus 8.6 mg. per cent, total protein 4.5 Gm. per cent, and albumin/globulin ratio 2.8/1.7. On day 9, a glucagon tolerance test was performed after a 9 hour fast. The fasting sugar was 20 mg. per cent, 54 mg. per cent at 30 minutes, and 25 mg. per cent at 90 minutes. Epinephrine (0.08 c.c.) 1:1,000 given intramuscularly 2 hours after the glucagon produced no hyperglycemic response (Fig. 3).

On day 16, a casein tolerance test was performed after a 9 hour fast. The initial blood sugar was 30 mg. per cent. The patient ingested 1.5 Gm. per kilogram of calcium caseinate. The blood sugar was 31 mg. per cent at 15 minutes, 24 mg. per cent at 30 minutes, and 7 mg. per cent at 120 minutes (Fig. 3). There were no symptoms.

The infant fed well, gained weight, and became more alert. At age 3 weeks he appeared normal to examination and weighed 2,750 grams. The blood sugar remained in the range of 60 to 90 mg. per cent (TRS) 4 hours after feedings. He was discharged home on a 4 hour feeding schedule of an evaporated milk formula containing 10 per cent added carbohydrate.

During the infant's stay in the hospital, additional laboratory examinations were done. Cultures of the blood,

ventricular, subdural, and spinal fluids were negative. X-rays of the skull and chest were normal. Repeated urinalyses were unremarkable, with no glucosuria or acetonuria. Serum electrolytes were also normal.

Subsequent studies included another casein tolerance test at 32 days of age. After a 9 hour fast, the initial sugar was 44 mg. per cent. He ingested 1.5 Gm. per kilogram of calcium caseinate. Blood sugar levels at 60, 90, and 120 minutes were 44, 75, and 44 mg. per cent (Fig. 3). Subsequent fasting blood sugar levels were 80, 92, and 74 mg. per cent at 2½, 5 and 7 months of age, respectively. The patient had grown and developed normally during this time.

CASE 2.—D. B. (HLH No. B-43864) (Fig. 2), a 2,140 gram Negro male, was born on Aug. 26, 1957, 25 days prior to the expected date of confinement. The mother was a 19-year-old Rh positive primipara, with a negative serologic test for syphilis, first seen at 27 weeks' gestation. She was hospitalized for 3 weeks at this time because of a blood pressure of 170/112, 30 pound weight gain, generalized edema, and frontal headache. She was given 55 Gm. of magnesium sulfate intramuscularly over a 3 day period. Reserpine was given thereafter. On a low salt diet and bed rest, she lost 9 pounds and the blood pressure was 150/105 at discharge. Eleven days later, she was readmitted for epigastric pain and vomiting. The blood pressure was 126/84, urine negative. On bed rest, she improved slowly and one week later, a medical induction of labor was attempted by stripping the membranes. Two days later active labor began. The blood pressure rose to 169/110 and she was given 5 Gm. of magnesium sulfate intramuscularly. Labor lasted 5⁷⁄₆₀ hours with a second stage of ³⁴⁄₆₀ hours. The membranes ruptured spontaneously ¾ hour prior to delivery. The placenta weighed 470 grams and had many small infarcts on the maternal and fetal surfaces. The blood pressure immediately post partum was 130/95 and at 6 weeks 110/70.

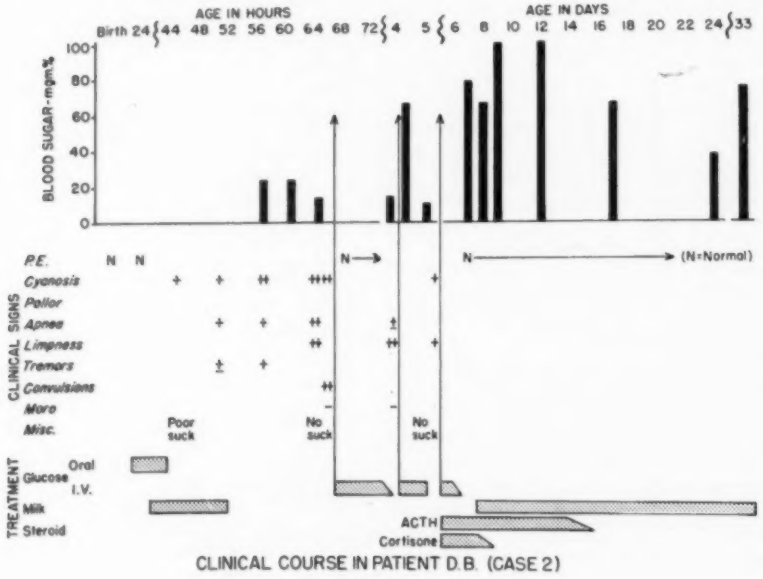


Fig. 2.

The infant was born spontaneously in vertex presentation. He breathed and cried in 10 seconds. His immediate condition was "excellent" and physical examinations at birth and at 7 hours of life were normal. Because of his prematurity, the baby was given nothing by mouth for 24 hours and then begun on glucose water. His body temperature remained low and he was put into a Gordon-Armstrong Incubator at 25 hours of age. He did well until 44 hours of age at which time he fed poorly, was cyanotic when sucking, and had poor muscle tone. At 52 hours of age, the baby was found apneic and pulseless, but was resuscitated by manual stimulation.

At 56 hours of age there was a recurrence of the apnea with severe bradycardia, and a weak heartbeat. His cry was high pitched and tremors of the right arm were noted. The apnea responded well to epinephrine and caffeine-sodium benzoate, parenterally. Blood obtained at this time showed a sugar level of 24 mg. per cent (TRS), nonprotein nitrogen 44 mg. per cent, calcium 8.7 mg. per cent, phosphorus 8 mg. per cent, sodium and potassium normal. Lumbar puncture was unremarkable except for a cerebrospinal fluid sugar of 15 mg. per cent. Subdural taps yielded no fluid. At 61 hours the blood sugar was 24 mg. per cent, and the infant was given 100 meg. of glucagon intravenously. The blood sugar was 5 mg. per cent at 63 hours of age (Fig. 3). Physical examination at this time revealed the infant to be alert, active, and crying vigorously. One hour later, however, the baby was again cyanotic, limp, with an apical pulse of less than 40 per minute, and no visible respirations. Vigorous physical stimulation initiated only isolated gasping movements. He responded this time only after endotracheal intubation and mouth-to-tube resuscitation, and intramuscular epinephrine. The blood sugar level was 18 mg. per cent. An intravenous infusion of 10 per cent glucose was started, but the baby began having quadrilateral jerking movements. These were temporarily controlled with 5 c.c. of 50 per cent glucose and phenobarbital. He was hyperreactive to stimuli.

At the age of 72 hours, the infusion infiltrated and the infant had a generalized clonic seizure which responded to 10 per cent glucose intravenously and phenobarbital intramuscularly. Throughout the fourth day of life he did well and the infusion was discontinued. About 2 hours later he became apneic, limp, and unresponsive. The blood sugar level (TRS) was 14 mg. per cent. He responded promptly to 10 c.c. of 50 per cent glucose with a return of muscle tone and response to stimuli. The infant was subsequently maintained on an infusion of 10 per cent glucose with added electrolytes, and feedings of 15 per cent glucose by intragastric tube.

On the fifth day of life the infant was still quite lethargic, with blood sugar levels ranging from 10 to 33 mg. per cent (TRS) despite temporary rises to 60 mg. per cent following glucagon and epinephrine (Fig. 3). He was unresponsive, dusky, and limp. Because he seemed to be suffering an intractable hypoglycemia, 50 mg. of Solu-Cortef was given intravenously and 20 units of ACTH intramuscularly. His clinical response was remarkable with restoration of skin color and muscle tone. Thereafter 2 to 4 hour fasting blood sugar levels were 60 to 100 mg. per cent (TRS).

On the sixth day of life the intragastric tube was removed and nipple feedings of evaporated milk and water 2:3 with 5 per cent added carbohydrate begun. Thereafter the infant did well. Cortisone was tapered and discontinued by the eighth day of life, and ACTH by the sixteenth. Blood sugar levels after 4 to 8 hour fasts were 64 to 120 mg. per cent during this time. Numerous urine examinations were normal, as were blood chemistry determinations. A casein test meal on the twenty-fourth day of life did not affect the blood sugar (Fig. 3). On the twenty-fifth day of life he was discharged weighing 2,220 grams. A leucine tolerance test was normal at

33 days of age (Fig. 3). Fasting blood sugar levels at 3, 10, and 11 months were 62 to 76 mg. per cent. At 11 months he had grown and developed normally.

Clinical Summary of the 8 Cases.—As noted in Table I all of the mothers had mild pre-eclampsia, consisting of hypertension in all, albuminuria in 4, and excessive weight gain in 2. The medications used in the treatment of the pre-eclampsia are detailed in the case reports and were not uniform.

All the infants did fairly well until the onset of symptoms at 40 to 57 hours of age (Table II). Initial symptoms were listlessness and refusal of feedings after milk had been taken well. Apnea and loss of muscle tone followed and after a variable period of time, cyanosis, tremors, and convulsions ensued. Blood sugar levels at the time of convulsions ranged from 1.0 to 24 mg. per cent. In 5 infants the spinal fluid sugar ranged from 0 to 15 mg. per cent and, in several, first

TABLE I. SUMMARY OF 8 CASES OF SYMPTOMATIC NEONATAL HYPOGLYCEMIA ASSOCIATED WITH TOXEMIA OF PREGNANCY

CASE	SEX	RACE	GESTATION (WEEKS)	MOTHER'S PRENATAL COURSE	COMPLICATIONS OF LABOR AND DELIVERY	BIRTH WEIGHT (GRAMS)
B. M.	M	W	36½	Severe weight gain Mild hypertension	Adherent clot over one-third of placenta	2,580
D. B.	M	C	36½	Severe pre-eclampsia	Induction of labor Precipitate delivery	2,140
P. B.	M	W	37	Moderate hypertension Albuminuria	Uterine inertia with intrapartum hemorrhage. Cesarean section	2,310
G. A.	F	C	38	Hypertension Albuminuria	Prolonged ruptured membranes Breech presentation	1,360
F. Z.	M	W	39	Excessive weight gain Hypertension	Precipitate delivery	2,095
R. F.	F	W	37?	"Slight" hypertension	None	1,500
R. T.	M	C	38	Hypertension Albuminuria	Prolonged second stage	3,090
B. D.	M	W	32	Hypertension Albuminuria	None	1,812

Additional complications in the individual pregnancies included an adherent placental clot (B. M.), induction of labor and precipitate delivery (D. B.), uterine inertia, intrapartum hemorrhage, cesarean section, and multiple birth (P. B.), breech extraction and prolonged ruptured membranes (G. A.), precipitate delivery (F. Z.), and a prolonged second stage of labor (R. T.). Two (R. F. and B. D.) had no known complications of labor or delivery. Seven infants were delivered vaginally, one by cesarean section. All but 2 were premature by weight although in 7 cases the length of gestation was 36½ weeks or more.

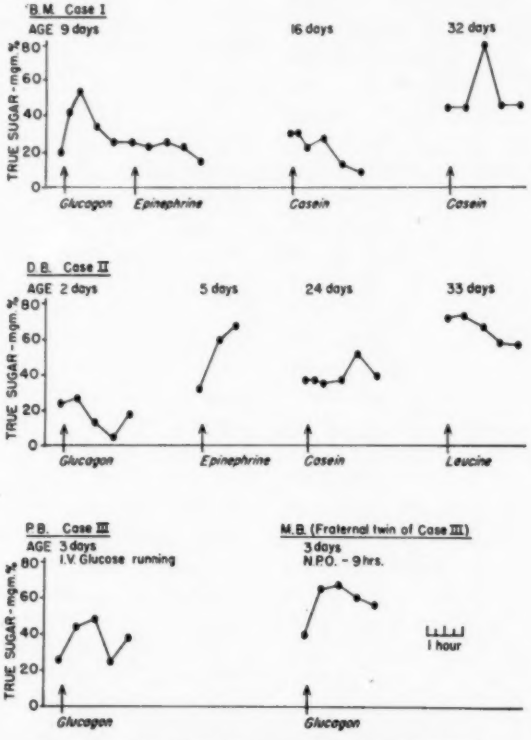
suggested the diagnosis of hypoglycemia as a cause for symptoms. Administration of parenteral glucose alleviated symptoms immediately in every infant and was necessary for prolonged periods of time to maintain normal blood sugar levels. Despite these measures, 5 infants had occasional low blood sugar, without symptoms, for varying periods of time. In 5 (B. M., D. B., P. B., R. F., and B. D.) the course was self-limited and benign although one (D. B.) required ACTH and cortisone to control the hypoglycemia. These 5 were developing normally at last examination. Two other infants (G. A. and R. T.) are

spastic and mentally retarded, and one other (F. Z.) died at 17 days of life of generalized Pseudomonas sepsis and early toxoplasmosis.

Results of Tolerance Tests.—Various tolerance tests were performed in an attempt to elucidate the etiology of the hypoglycemia observed. These included the administration of glucagon or epinephrine as a test for available hepatic glycogen and of casein or leucine as a test for hypoglycemia precipitated by amino acids.[14]

gestion of Casec resulted in a marked hypoglycemia (Fig. 3). By the thirty-second day of life, however, the casein tolerance test was normal. The significance of the apparent transient sensitivity to casein is difficult to interpret since no tests on normal infants are available for comparison.

In D. B. (Case 2), glucagon administered at the time of symptoms had no effect on the blood sugar, which continued to fall to very low levels (Fig. 3). A similar failure to respond



EFFECT OF VARIOUS SUBSTANCES ON BLOOD SUGAR

Fig. 3.

In the first patient, B. M., the intravenous glucagon tolerance test on the ninth day was normal (Fig. 3). Epinephrine following glucagon had no hyperglycemic effect, suggesting a limited quantity of available glycogen in the liver. On day 16, the oral in-

to glucagon has been observed during the immediately postnatal rapid fall in blood sugar in infants of diabetic mothers.[15] By the fifth day of life, epinephrine resulted in a good hyperglycemic response (Fig. 3). Casec on the twenty-fourth day of life had no

TABLE II. SUMMARY OF THE COURSE OF 8 INFANTS WITH SYMPTOMATIC NEONATAL HYPOGLYCEMIA

CASE	CONDITION AT BIRTH	AGE AT ONSET OF SIGNS (HOURS)	SYMPTOMS AND SIGNS					SUGAR CONCENTRATION AT SYMPTOMS		IMMEDIATE RESPONSE TO INTRAVENOUS GLUCOSE	OUTCOME
			CYANOSIS	LIMPNESS	TREMOR	APNEA	CONVULSIONS	CSF (MG. %)	BLOOD (MG. %)		
B. M.	Fair	47	x	x	x		x	-	20*	+	Normal at age 10 months
D. B.	Good	44-52	x	x	x	x	x	15	24* 14 1	+	Well at age 11 months
P. B.	Fair to poor	57	x			x	x	12	6*	+	Well at 9 months. Development equal to that of fraternal twin
G. A.	Good	40-48				x	x	0	4	+	Spastic and jittery at 4 months. Convulsions with normal blood sugar
F. Z.	Fair	44	x		x	x	x	2	2	+	Died at 17 days of Pseudomonas sepsis and toxoplasmosis
R. F.	Good	48-72				x	x	0	18*	+	Well at last follow-up at 5 months
R. T.	Good	46	x		x	x	x	-	1	+	Severely retarded, spastic with myoclonic seizures. Institutionalized at 3 years
B. D.	Good	40	x		x		x	-	24-18*	+	Well at discharge 44 days old

*Total reducing substance.

appreciable effect on the blood sugar, whereas leucine on day 33 resulted in a minimal fall in the blood sugar (Fig. 3).

The fraternal twins (see Appendix, cases P. B. and M. B.) received glucagon on the third day of life, after the symptoms of hypoglycemia had been controlled by parenteral glucose in P. B. Each had a significant and comparable rise in blood sugar suggesting available glycogen in the liver. Of interest was the fact that, although P. B. was receiving an infusion of glucose prior to and during the test, his initial blood sugar was 26 mg. per cent, whereas that of his fasting brother (M. B.) was 40 mg. per cent.

DISCUSSION

Hypoglycemia in the newborn period is rarely associated with clinical signs. However, of 25 cases of chronic idiopathic spontaneous hypoglycemia in infants and children reported by McQuarrie,[9] 2 became clinically evident during the first day of life and another in the first week. Schwartz and associates[11] described a case of hypoglycemia which had commenced with convulsions in the thirty-fifth hour of life and had persisted for 17 months at the time of the report. In another case of manifest hypoglycemia in a neonate, an islet-cell adenoma was discovered at autopsy.[12] Moreover, glycogen storage disease of the liver can also be responsible for symptomatic hypoglycemia with convulsions on the third day of life.[10] In all these cases, the cyanosis, limpness, jitteriness, apnea, coma, and convulsions which were observed were similar to the symptoms seen in older patients with hypoglycemia. Thus it would appear that while hypoglycemia in the newborn rarely produces discernible signs, some infants do present clinical manifestations of low levels of circulating glucose. In the 8 cases reported here, convulsions, apnea, tremor, and limpness were associated with a marked hypoglycemia on the second or third day of life and the clinical syndrome was alleviated immediately by the administration of parenteral glucose. It is noteworthy that 5 of the infants subsequent to treatment had very low blood sugar levels unassociated with apparent symptoms or signs. Whether this reflects a clinical tolerance to hypoglycemia or additional factors affecting the response of the central nervous system to low glucose levels is uncertain. The initial response of all of the infants to parenteral glucose is evidence that the hypoglycemia observed was responsible for the symptoms and signs. The unusual features in the cases reported are the self-limited, but quite refractory, course, the fact that 6 of the 8 infants were premature by weight, and the association with pre-eclampsia in the mother.

A relatively short, self-limited course is not common with any of the known forms of symptomatic hypoglycemia outlined by Conn and Seltzer.[16] Organic causes such as hyperinsulinism, hepatic disease, glycogen storage disease, or adrenal or pituitary hypofunction seem unlikely to account for such a course. Central nervous system lesions such as those in G. A. and R. T. may cause hypoglycemia,[17] but these lesions may also be a result of hypoglycemic attacks. Six infants showed no evidence of cerebral damage. All the infants had been fed prior to the episodes of hypoglycemia, consistent with the possibility that a Staub-Traugott phenomenon[9] had led to the symptoms; however, 5 of the infants also had low

blood sugars when fasting. Idiopathic hypoglycemia as described by MeQuarrie[9] is of longer duration, and usually requires long-term ACTH or cortisone therapy for maintenance of normoglycemia. This measure was required in only 3 of the 8 cases described here and for relatively short periods.

Despite being close to term by date, 6 of the infants weighed less than 2,500 grams. In the case of the fraternal twins (P. B. and M. B.) it was the smaller who had hypoglycemia. The hypoglycemia of the first day of life is greater in prematures than in full-term infants, especially under stress.[2] Norval[2] followed the blood sugar in 42 premature infants of whom 9 died. Four of the infants who died had blood sugar levels in the range of 4 to 20 mg. per cent. In addition to delayed feedings, other factors which might contribute to a relative hypoglycemia in prematures include inadequate hepatic glycogen stores, inability to mobilize glycogen,[18] and an inefficient regulation of glucose metabolism. These factors may reflect enzymatic immaturity. The diminished ability of the liver of the premature infant to conjugate bilirubin[19] or sulfonamide[20] and to oxidize tyrosine[21] are examples of enzymatic immaturity. In animals, glucose-6-phosphatase activity in the liver is markedly diminished prior to birth.[22] All of these apparent deficiencies become less evident as the infant matures. The self-limited course of the hypoglycemia observed in the cases reported is consistent with the theory that an adaptation or maturation of enzymes has occurred.

The mothers of all 8 infants in this report had pre-eclampsia. It is known that infants delivered of women with toxemia of pregnancy have an increased morbidity and mortality,[23-27] especially if there is an associated complication of labor or delivery. In addition, premature delivery frequently occurs in toxemic pregnancies, partly because of complications such as placental hemorrhage and premature rupture of the membranes and partly because of early inductions as an obstetric measure to protect the health of the mother. Premature infants born to toxemic mothers have a lower mortality rate than other prematures during the first day of life, but a higher mortality rate over the first week.[28] They are more often edematous, feed poorly, and gain weight more slowly.[29] Their blood urea nitrogen is higher.[30] Neonatal cyanotic attacks are frequently associated with pre-eclampsia in the mother.[31] The increase in morbidity may be partly associated with the administration of drugs such as barbiturates, morphine, and the hexamethonium compounds[32] to the mother, but for the most part its cause is unknown. This report of 8 cases of symptomatic neonatal hypoglycemia, in all of which the mothers had suffered some manifestations of pre-eclampsia, suggests the possibility that some of this morbidity may be due to unrecognized attacks of hypoglycemia. The need for more careful observation of these infants in the nursery is apparent.[33]

Why pre-eclampsia in the mother, often together with some other complication of labor and delivery and low birth weight, should be associated with symptomatic hypoglycemia on the second day of life is obscure. Abnormal diabetic-type glucose tolerance curves have been observed in toxemic mothers[34] but the small birth weights of these infants make it unlikely that

they are offspring of prediabetic mothers. What effect the pre-eclampsia might have on glycogen stores or glucose metabolism in the fetus and neonate is unknown. Whether or not more subtle difficulties such as reading disabilities, cerebral palsy, and behavior disorders, all observed in increased incidence in products of toxemic pregnancies,[35, 36] are related to hypoglycemia, deserves further investigation.

Finally, much has been written to imply that low blood sugar levels in the newborn are not of clinical significance.[37, 38] Since hypoglycemia can be responsible for apnea, cyanosis, limpness, and convulsions in the neonate, it should be considered in the differential diagnosis of these signs in the offspring of toxemic women.

SUMMARY

1. Eight cases of symptomatic hypoglycemia with apnea, cyanosis, coma, and convulsions have been described which occurred in infants of 2 days of age delivered of mothers with pre-eclampsia.

2. Recovery from hypoglycemia took place once the blood sugar levels were exogenously supported.

3. Five infants had no apparent sequelae; 2 infants have permanent central nervous system damage; and one died at 17 days.

4. The implications of these findings in relation to the increased morbidity and mortality in offspring of toxemic mothers have been discussed.

APPENDIX

Case Reports.—

P. B. (JHH No. 61 8650), a 2,310 gram white male infant, was the second-born of fraternal twins on Nov. 21, 1957, 21 days prior to the expected date of confinement. The mother, a 23-year-old, Rh-positive primipara, with a negative serologic test for syphilis, was followed by her private obstetrician from the ninth week of gestation. The entire prenatal course was uneventful with blood pressure readings of 120-140/70-80. At 37 weeks' gestation, she was admitted in active labor with spontaneously ruptured membranes of 6 hours' duration. On admission, her blood pressure was 160/106 and narrowing of the retinal vessels was noted. No edema or albuminuria was present. Labor progressed poorly. She received, intramuscularly, magnesium sulfate (a total of 15 Gm. over 6 hours) and Demerol. After 17 hours of labor, Pitocin was given intravenously over a 2½ hour period with poor results. Because of intrapartum bleeding and uterine inertia, an emergency cesarean section was performed under local anesthesia. The placenta weighed 855 grams and was normal.

This infant was the second-born of fraternal twin boys delivered several minutes after his sibling. He cried at birth, but respirations were inadequate for 3 minutes. His initial condition was described as "poor" with cyanosis and poor muscle tone. A Grade 1 systolic murmur was noted. The infant was placed in an Isolette incubator, with full humidity and oxygen (35 per cent) and was given penicillin and streptomycin.

At 24 hours of age he was started on routine breast feedings, along with supplements of 5 per cent glucose and water. He nursed fairly well. During the second day of life he sucked poorly. At about 57 hours of age, while at the breast, he began having forceful gasping respirations, and became cyanotic. He responded to oxygen, suction, and parenteral caffeine-sodium benzoate, and became active and alert. Six hours later a generalized seizure occurred, consisting of rhythmic contractions of all four extremities, lasting 1½ minutes, followed by opisthotonus, with facial contractions and apnea lasting

30 seconds and urination. After the seizure he was hyperreactive and had an exaggerated Moro reflex. A lumbar puncture yielded xanthochromic fluid with 82 red blood cells and 2 round cells per cubic millimeter. The cerebrospinal fluid sugar was 12 mg. per cent, protein 100 mg. per cent, and Pandy reaction 3 plus. A white blood cell count was 2,300. Blood and cerebrospinal fluid cultures were negative.

At 66 hours of age the blood sugar was 6 mg. per cent (TRS) and the serum calcium 12.7 mg. per cent. After several cubic centimeters of 50 per cent glucose were given by gastric tube, the blood sugar rose to 14 mg. per cent (TRS). An infusion of 10 per cent glucose was started intravenously. At 72 hours of age the infusion infiltrated and the infant had a second hypoglycemic episode, similar to the first. The 10 per cent glucose infusion was started again and quickly abolished the hyperactivity and jitteriness and restored the baby's color. Blood chemistry determinations at this time were: sugar, 30 mg. per cent (TRS), sodium 150, potassium 4.3, chloride 115, and carbon dioxide 30 mEq. per liter. At 80 hours of age, with the infusion running, the blood sugar was 26 mg. per cent (TRS). After glucagon (30 meg. per kilogram) was administered intravenously, the sugar levels were 50 mg. per cent (TRS) at one hour and 38 mg. per cent (TRS) at 2 hours (Fig. 3). The infant remained in good condition thereafter, with no abnormal physical findings despite blood sugar levels ranging from 11 to 26 mg. per cent (TRS). On the fifth day of life the infusion was continued and oral glucose feedings added. Blood chemistry determinations were normal and sugar levels ranged from 44 to 76 mg. per cent. The infusion of glucose and electrolytes was discontinued on day 8 and routine formula feedings instituted on day 9. Blood sugar levels after 2 to 4 hour fasts ranged from 38 to 50 mg. per cent (TRS) on the ninth to the thirteenth day of life. On the ninth day a casein tolerance test was indeterminate because of an initially low fasting blood sugar level of 9 mg. per cent. He had no symptoms.

On the sixteenth day of life the infant weighed 2,235 grams and was discharged on an evaporated milk formula. He had been followed by his private pediatrician. At 3½ months of age, a 9 hour fasting blood sugar level was 50 mg. per cent. At 7 months his development was normal, his height and weight were the same as those of his fraternal twin.

M. B. (JHH No. 618650), a 2,660 gram white male infant, was the *nonaffected fraternal twin brother of P. B.* born several minutes earlier. He breathed and cried immediately. Physical examination was normal except for a Grade 1 systolic murmur. He was placed in an incubator with humidity and oxygen, and given penicillin and streptomycin. He was breast fed and received glucose water supplements starting at 24 hours. His course was benign and he never showed any signs of jitteriness or convulsions. On the third day of life food was withheld 9 hours prior to a glucagon tolerance test. The fasting sugar level was 41 mg. per cent and glucagon (30 meg. per kilogram) was given intravenously. Blood sugar was 66 mg. per cent at 30 minutes, 67 mg. per cent at 60 minutes, and 56 mg. per cent after 2 hours (Fig. 3). A casein tolerance test on the sixth day of life was normal. He was discharged on the seventh day of life, at a weight of 2,300 grams, taking breast feeding. At age 3½ months, the blood sugar after an overnight fast was 55 mg. per cent. At 7 months his development was normal.

G. A. (BCH No. 241033), a 1,360 gram Negro female, was born on March 13, 1958, 10 days prior to the expected date of confinement. The mother was a 30-year-old, Rh-positive, para 2113, with a negative serologic test for syphilis. She was first seen at 18 weeks' gestation and had an uneventful prenatal course; the blood pressure was 120-140/60-80. Because

of ruptured membranes she was admitted at 38 weeks' gestation and found to have a blood pressure of 150/100, 4 plus albuminuria, and brisk reflexes. She went into spontaneous labor and received phenobarbital and magnesium sulfate (20 Gm. total intravenously) during labor which lasted $7^{33}/_{60}$ hours. The second stage of labor was 33 minutes. The infant was delivered as an assisted frank breach. The blood pressure was 130/90 3 days after delivery. The infant breathed and cried at birth and was in good condition. She was placed in an incubator with humidity and oxygen and was given vitamin K.

Her condition remained good throughout her first day. At 34 hours of age nipple feedings of glucose water were begun. At 40 hours of age a shrill cry was noted. At 48 hours she had a generalized clonic seizure. Physical examination afterward was unremarkable. A lumbar puncture yielded clear, slightly xanthochromic fluid containing no sugar, a protein of 144 mg. per cent, and a chloride of 119 mEq. per liter. Blood chemistry determinations at this time were: sugar 4.0 mg. per cent, calcium 8.0 mg. per cent, sodium 131, potassium 6.0, and carbon dioxide 24.3 mEq. per liter.

The infant became cyanotic and apneic. The trachea was suctioned under direct vision and the infant revived by mouth-to-mouth insufflation. Twenty-five cubic centimeters of 10 per cent glucose were given rapidly intravenously, followed by 3.0 c.c. of 10 per cent calcium gluconate. Within 10 minutes her color was good and she was very active. She was given phenobarbital, penicillin, and streptomycin, and a continuous infusion of 10 per cent glucose with added electrolytes. Cortisone, 5 mg. every 6 hours, and ACTH, 4 units every 8 hours, were started at this time. She was digitalized. Throughout the next few hours, the infant remained in good condition. A chest film was negative. The blood sugar stabilized at 57 to 60 mg. per cent.

Over the next several days the infant was maintained on dilute half-skimmed milk with added carbohydrate, administered by gavage. Sugar levels remained around 60 mg. per cent. However, because of coffee-ground emesis, the ACTH was discontinued on the seventh day of life. She did fairly well and gained slowly.

On the fifteenth day of life, she was again noted to have a shrill cry and increased tone, and to be hyperkinetic. Two hours later a blood sugar determination was 7 mg. per cent. She was fed and a repeat blood sugar was 27 mg. per cent, the sodium 135, chloride 91.5, and potassium 6.2 mEq. per liter. Total serum proteins were 6.3 Gm. per cent. After an intravenous infusion of glucose and water was started the hypertonic signs gradually cleared. ACTH, 4 to 12 units daily, was reinstituted and maintained for the subsequent 2 months. Blood sugar levels obtained at random ranged from 37 to 128 mg. per cent. While she was receiving ACTH, glucose occasionally appeared in the urine.

Her course for a time was uneventful. She ate well and gained slowly. On the sixty-third day of life she weighed 2,150 grams. A preprandial sugar level was 14 mg. per cent and a 2 hour postprandial, 14 mg. per cent. Four days later blood sugar levels at similar times were 63 and 119 mg. per cent.

On the seventy-second day of life, while still receiving ACTH, the infant had two successive generalized clonic seizures, each of a few seconds' duration. The eyes deviated to the left, and she drooled saliva. Blood sugar at this time was 63 mg. per cent. Several times in the next 2 days she had similar seizures. Blood sugar levels obtained before as well as after some of these seizures were repeatedly 81 to 115 mg. per cent. She was started on phenobarbital. The ACTH was slowly tapered and was discontinued on the eighty-first day of life.

No further seizures occurred after the seventy-third day of life but she

remained hyperirritable and spastic. An electroencephalogram was consistent with a diagnosis of idiopathic convulsive disorder.

F. Z. (HLH No. B52410), a 2,095 gram white male infant, was born on June 4, 1958, 4 days prior to the expected date of confinement. The mother was a 40-year-old, Rh-positive, para 3104, with a negative serologic test for syphilis. She had had mild hypertension during her previous 3 pregnancies. Her first prenatal visit, at 28 weeks' gestation, revealed a blood pressure of 140/90, but no edema or albuminuria. Serpasil was given orally for the elevated blood pressure with good response. At term, the mother was admitted in active labor with ruptured membranes of questionable duration. After 9 hours of labor, the patient went suddenly from a cervical dilatation of 2 cm. to completion of the second stage labor in 6 minutes. She received no medication or anesthesia. Her blood pressure ranged from 145-160/90-100 during labor and was 132/76 at discharge 3 days post partum.

The infant was born spontaneously in vertex presentation. After an initial gasp, he did not breathe or cry for 2 minutes. His immediate condition was "fair." He was placed in a Gordon-Armstrong Incubator. At 4 hours of age he was pink and active, with a good cry, suck, and Moro reflex. Except for occasional hypothermia and jitteriness, he did well for the first 40 hours of life. At this time he was begun on glucose water feedings.

At the age of 44 hours, while being fed, a generalized tonic-clonic convulsion occurred, associated with breath-holding lasting 15 seconds. Subsequently he was drowsy and restless. There were spontaneous tremors of the arms and legs. When 47 hours old he had a similar apneic convulsive episode, accompanied by marked cyanosis, lasting 30 to 45 seconds. A transient left facial palsy was detected, along with tremors, mainly of the left arm. The blood sugar was 2 mg. per cent and calcium 11.7 mg. per cent. Lumbar puncture yielded a very slightly xanthochromic fluid with 2 mg. per cent sugar, a negative Pandy reaction, and 2 cells per cubic millimeter. The child was given 2 c.c. of 50 per cent dextrose in water intravenously and an infusion of 10 per cent dextrose was begun. Within 5 minutes he was less jittery, breathing deeply, and had better color. Physical examinations were unremarkable, except that no Moro reflex could be elicited. The liver was palpable one fingerbreadth below the costal margin. The urine was normal.

The third day of life was uneventful. His infusion was continued, and was supplemented with oral feedings of an electrolyte mixture in 10 per cent dextrose. Blood chemistry determinations were calcium 10.5 mg. per cent, phosphorus 5.0 mg. per cent, sodium 134, chloride 95.2, and potassium 4.3 mEq. per liter. The bilirubin was 9.6 mg. per cent (direct 3.9 mg. per cent), serum protein 5.6 g. per cent, with albumin 3.2 and globulin 2.4 Gm. per cent. Several random blood sugar determinations ranged from 6 to 173 mg. per cent.

He was kept on oral feedings thereafter and showed no more evidence of hypoglycemia, either clinically or chemically. He remained jaundiced, however, had diarrhea with greenish stools, and had an irritated infected rash about the umbilicus and genitals. He was given chloramphenicol, penicillin, special feedings, and general supportive care. On the tenth day of life x-rays showed right upper and lower lobe pulmonary infiltrates which remained unchanged on subsequent films. The infant became lethargic and poorly responsive; the liver was palpable 2 fingerbreadths below the costal margin. His condition deteriorated progressively thereafter, and he died on June 20, 1958, when 17 days old.

Autopsy revealed generalized *Pseudomonas aeruginosa* sepsis with multiple areas of necrosis and mild early toxoplasmosis.

R. F. (HLH No. A-63667), a 1,550 gram white female child, was born on June 19, 1948, 1 to 3 weeks prior to the expected date of confinement. Results of the serologic test for syphilis on the mother were unknown, but the infant proved to be STS negative. The mother was a 20-year-old primipara. Because of hypertension she had been given a low salt diet during her one visit to a prenatal clinic. The infant was born at home spontaneously in vertex presentation with the assistance of a midwife. The infant breathed and cried immediately. Because of her small size she was brought to the Harriet Lane Home premature nursery. On admission at age 1 hour she was in excellent condition.

The infant was started on glucose water the first day of life, and on a dilute half-skimmed milk formula with added carbohydrate the second day. On the third day of life the child suddenly developed poor color, irregular respirations, and convulsions. Subdural taps yielded no fluid. A lumbar puncture was unremarkable, except that no sugar was found in the spinal fluid. The blood sugar was 18 mg. per cent (TRS). Two cubic centimeters of 50 per cent glucose were given intravenously, with immediate cessation of symptoms. Blood sugar at 62 hours was 46 mg. per cent (TRS). Repeated doses of intravenous glucose had to be given in order to maintain the sugar level as high as 40 mg. per cent. At 80 and 104 hours of life the blood sugar was 18 mg. per cent (TRS). No symptoms were noted on either occasion. The epinephrine tolerance test showed a normal hyperglycemic response. On one occasion a half-hour postprandial sugar level was 72 mg. per cent (TRS), but most of the half-hour postprandial sugar levels ranged from 32 to 40 mg. per cent (TRS). The nonprotein nitrogen was 46 mg. per cent, calcium 9.6 mg. per cent, phosphorus 5.2 mg. per cent, sodium 141 and carbon dioxide 26.6 mEq. per liter. No further convulsions occurred, but because of recurrent low blood sugar, adrenal cortical extract administration was begun on the fifth day. A three hour postprandial blood sugar was again below 20 mg. per cent (TRS), and a 2 hourly feeding schedule was utilized, with a dilute half-skimmed milk formula. By the tenth day the infant was doing quite well and having no further convulsions. She seemed extremely hungry, and was given a high calorie intake. On the nineteenth day adrenal cortical extract was discontinued. As the period between feedings was gradually lengthened her blood sugar levels were again as low as 16 to 18 mg. per cent (TRS) on several occasions as late as the thirty-first day of life. Two glucose tolerance tests and an insulin tolerance test were normal. Because of the recurrence of the hypoglycemia, adrenal cortical extract administration was reinstituted at about 1 month of age, and maintained again for 10 days. From this time on the blood sugar gradually increased into the normal range. By 5 weeks of age she was doing well on 3 hourly feedings, and by 10 weeks on 4 hourly feedings. At 12 weeks, after an 8 hour fast, the blood sugar was 68 mg. per cent (TRS).

On the ninety-eighth day, weighing 3,900 grams, the child was discharged. She was seen several times thereafter in the outpatient department, and when lost to follow-up after 6 months of age was doing well. No further blood sugar determinations were obtained.

R. T. (BCH No. 235175), a 3,090 gram Negro male infant, was born on Feb. 14, 1955, 5 days prior to the expected date of confinement. His mother, an Rh-positive, 16-year-old primipara, with a negative serologic test for syphilis, had hypertension (blood pressure 125/100) and 3 plus albuminuria for at least a week prior to delivery. The total length of labor was $8^{53}/_{60}$ hours with a second stage of $1^{23}/_{60}$ hours. The infant was delivered by elective low forceps over a

median episiotomy. The mother received intramuscular magnesium sulfate (10 Gm.) during labor. The postpartum blood pressure was 120/80 and urine normal. The baby was in good condition at birth.

At 13 hours of age the infant was started on 4 hourly breast feedings. At the forty-sixth hour of life, he was found cyanotic, apneic, and stiff, with arms and legs shaking. His heart rate was 80 per minute. He was resuscitated with mask oxygen and manual stimulation. Over the next several hours he had repeated episodes of apnea and cyanosis, but always responded when stimulated. There was apparent marked peripheral vasoconstriction. He was kept in a humid incubator with oxygen and given penicillin and streptomycin. When 52 hours old, his blood sugar was found to be 1.0 mg. per cent. Fifteen cubic centimeters of 50 per cent glucose was given intravenously with immediate improvement in respirations and an increase in the heart rate from 110 to 150 per minute. The child became more alert and his cyanosis disappeared. A venous cut-down was done, and an infusion of 5 per cent glucose containing 10 mg. hydrocortisone was begun. At this time blood chemistry determinations were: sodium 155, potassium 6.5, and chloride 115 mEq. per liter, serum protein 6.0 Gm. per cent, with albumin/globulin ratio of 3.2/2.8, alkaline phosphatase 3.6 Bodansky units, bilirubin 13.8 mg. per cent (direct 1.4 mg. per cent), carbon dioxide 21 mEq. per liter, calcium 10.4 mg. per cent, and blood urea nitrogen 34.6 mg. per cent. The urine was unremarkable.

Over the next day the child seemed better, but early on the fourth day of life he had a convulsive seizure, accompanied by cyanosis and very cold extremities. When 50 per cent glucose was pushed into the infusion he became more active and responsive but remained hypertonic. Later that day he repeatedly vomited, including one emesis of blood-streaked material. Serum electrolytes and blood sugar levels with the infusion running were normal. On the seventh day of life the infusion was discontinued, but hydrocortisone was continued through the eleventh day. Oral feedings were begun. He remained quite spastic but had no further convulsions. Random blood sugar levels were in the range of 42 to 58 mg. per cent and serum electrolytes were normal. During the second week of life an episode of diarrhea occurred. An abscess on the left leg had to be incised and drained, and he was treated with Terramycin. By the fourth week of life feedings were taken well and his weight was 3,230 grams but he was still quite hypertonic. On the twenty-fifth day of life he was discharged from the hospital.

The patient was seen frequently in the City Hospital pediatric clinic and observed to gain weight. He was retarded and spastic, however, and suffered myoclonic seizures. During his first 6 months serum chemistry determinations were repeatedly found to be normal with fasting blood sugar levels ranging from 38 to 50 mg. per cent. A sickle cell preparation was negative. Skull films were normal.

When 18 months old the baby was still having seizures, was spastic, and could not sit alone. He continued to progress poorly and when 3 years old was admitted to a home for retarded children.

B. D. (HLH No. A77855), a 1,812 gram white male child, was born on May 1, 1950, 8 weeks prior to the expected date of confinement. His mother, a 24-year-old, Rh-positive primipara, with a negative serologic test for syphilis, had 2-3 plus albuminuria and hypertension (160/90) for a month prior to delivery. Labor lasted 24 hours. The infant was delivered by elective low forceps. He breathed spontaneously and was said to be in good condition at birth.

The infant did well until 40 hours of age, at which time he spit up his feeding, became stiff, and had clonic

jerks. He was transferred to the Harriet Lane Home at this time. On arrival at 43 hours of age, he was jittery and mildly ieteric, but alert, with good color, and the physical examination was otherwise normal. Lumbar puncture revealed a normal cerebrospinal fluid except for a qualitatively low sugar. The blood sugar was 24 mg. per cent (TRS). The baby was given 5 per cent glucose orally every 4 hours.

He continued to be jittery. At 63 hours of age, spastic jerking movements followed by cyanosis and gasping respirations occurred. The blood sugar was 18 mg. per cent (TRS). Eight cubic centimeters of 50 per cent glucose was given intravenously with instantaneous improvement in respirations, color, and cry. At 66 hours of age, the blood sugar was 70 mg. per cent (TRS) and calcium 9.2 mg. per cent. The infant was started on 30 c.c. of 10 per cent glucose by gavage every 4 hours and developed loose stools. Two blood sugar levels between 66 and 100 hours of age were 72 and 62 mg. per cent (TRS). Evaporated milk feedings were started and tolerated well. He had no further episodes of apnea or seizures.

An intramuscular epinephrine tolerance test on the eighth day of life and an intravenous test on the tenth day of life showed no rise in blood sugar. The fasting level on the sixteenth day of life was 32 mg. per cent (TRS).

On day 19, an intravenous glucose tolerance test was normal. His fasting sugar at this time was 68 mg. per cent (TRS).

He was discharged on the forty-fourth day of life weighing 2,630 grams. No abnormalities were noted at this time.

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THE OUTCOME OF PREGNANCY IN DIABETIC WOMEN

I. Fetal Wastage, Mortality, and Morbidity in the Offspring of Diabetic and Normal Control Mothers

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THE complication of gestation by diabetes mellitus imposes considerable risks for the health of the mother and also greatly increases the fetal mortality rate (Pedowitz and Shlevin,[8] 1955, Clayton,[1] 1956, and Gellis and Hsia,[4] 1959). Usually, the control of diabetes during pregnancy becomes difficult and additional complications of gestation such as polyhydramnios and toxemia are common. Basing their reports on autopsy examinations, Kade and Dietel[5] (1952), Worm[9] (1958), and others estimated that the incidence of congenital malformations in the offspring of diabetic mothers is considerably higher than in the normal population. Dekaban and Magee[2] (1958) and Dekaban[3] (1959) described a number of children with various neurologic abnormalities and mental retardation who were born to diabetic mothers. In consequence of this finding it appeared worthwhile to test the hypothesis that the morbidity rate among the offspring of diabetic women is also higher than among children born to nondiabetic mothers.

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The present study was so designed as to investigate and analyze the total pregnancy wastage in 48 diabetic women as well as the abnormalities in the surviving offspring. The outcome of the pregnancies in the sample of 48 normal matched controls was evaluated in a similar manner as in the diabetic women. First, the data obtained from these two sample groups are evaluated and compared. Subsequently, various factors which might have been responsible for the less favorable outcome of the pregnancies in the diabetic women are analyzed. The detailed description and assessment of the abnormalities encountered in the offspring of diabetic mothers will be presented in Part II of this study; in Part I we are mainly concerned with statistical evaluation of the results obtained.

MATERIALS AND METHODS

The outcome of all pregnancies in 48 diabetic mothers was investigated. Of these, 17 were Caucasian and 31 were Negro women. The criteria of selection were as follows: (1) The diabetic mother had to be less than 43 years of age at the time the study was made. (2) She must have had at least two pregnancies after the diagnosis of diabetes was established. The main purpose of the latter criterion was to

eliminate the factor of a possibly increased risk for unfavorable outcome of pregnancy in the primipara (particularly in view of oversized babies born to diabetics), as a considerable proportion of our patients were juvenile diabetics. Since there are not many patients who can meet such requirements in any single institution, the patient material was drawn from a number of local hospitals, the names of which are given in the Acknowledgment. All mothers were interviewed by us and their medical records studied; we also examined personally most of the offspring. In those instances where no personal contact with the child could be obtained, a medical report from the family or school physician was secured. In 5 children we relied on the report from the school principal. Following office examination, 6 offspring required special investigation and they were hospitalized in an attempt to establish the nature of their disturbance in more detail.

The control mother for each diabetic mother was chosen from the same hospital in which the diabetic woman had her last delivery. The obstetric records for 3 months preceding this delivery were surveyed and that mother was accepted as a matched normal control who corresponded most closely to the diabetic woman in regard to race, age, number of pregnancies, and social status. The number of pregnancies in the normal controls was matched to the total of gestations in the respective diabetic mother before and after the diagnosis of diabetes.

Definition of Terms.—

1. *Mild degree of diabetes:* Diet only or diet and not more than 20 U. of insulin daily were sufficient for proper control of the diabetes between pregnancies.

2. *Moderate degree of diabetes:* Diet and 20 to 40 U. of insulin daily were required to afford satisfactory control.

3. *Severe degree of diabetes:* Diet and more than 40 U. of insulin were necessary for the control of the diabetes.

The control of the diabetes at the time of delivery was estimated as satisfactory if the urinalysis was normal or if it disclosed not more than a trace of sugar during the last 2 days of pregnancy and if the general condition of the mother was good; otherwise, the control of the diabetes at delivery was estimated as poor. Miscarriages and previable births were considered under one group—abortions; they encompassed all terminations of pregnancy under 26 weeks of gestation. Death within 4 weeks from birth was considered as a neontal death. Elevation of the maternal blood pressure during pregnancy above 160 systolic and above 90 diastolic on at least two occasions was taken as evidence of hypertension. The surviving offspring was regarded as abnormal if he had a severe congenital malformation or intellectual or neurologic deficit interfering seriously with his spontaneous activity appropriate for the age.

RESULTS

The sample of diabetic population consists of both Caucasian and Negro mothers but it is considered as one group for the purpose of analysis as it was felt that the differences were not sufficiently great in our group to warrant separate evaluation. However, to permit comparison, the pregnancy wastage and abnormal survivors of the two racial groups are listed separately in all tables.

The mean age of diabetic women at the time of this study was 31 years, 4 months and that of the normal controls was 30 years, 9 months. The mean age when the diagnosis of diabetes mellitus was established was 20 years, 4 months (Caucasians 14 years, 8 months; Negroes 23 years, 5 months). This indicates that a considerable proportion of our patients, particularly of Caucasian origin, were juvenile diabetics. The diagnosis of diabetes early in life also explains the fact that the incidence of pregnancies in Caucasian women before the diagnosis of diabetes was low. The total number of pregnancies before the diagnosis of diabetes was 78 (Caucasians 5, Negroes 73), with a mean of 1.3, whereas the total number of pregnancies after the diagnosis of diabetes was 157 (Caucasians 53, Negroes 104), with a mean of 3.2.

The state of diabetes between pregnancies was mild in 9 women (Caucasians 1, Negroes 8), moderate in 22 (Caucasians 11, Negroes 11), and severe in 17 (Caucasians 5, Negroes 12).

To decrease the risk of mortality in diabetic offspring, either induction of delivery or cesarean section 3 to 4 weeks prior to the estimated date of birth has recently become a common practice. In our material, however, there were only 9 induced births (Caucasians 4, Negroes 5) and 30 cesarean sections (Caucasians 14, Negroes 16) among 98 deliveries (abortions and premature births excluded).

Of the 157 pregnancies after the diagnosis of diabetes was made (Table I), 47 or 29.9 per cent resulted in abortion, 18 or 11.5 per cent in stillbirths, and 13 or 8.3 per cent of the infants died during the neonatal stage. Among the 79 surviving offspring (50.3 per cent of total pregnancies), neurologic or other abnormalities were present in 6, which amounts to 3.8 per cent of all 157 pregnancies or to 7.6 per cent of the surviving children.

In the total of 78 pregnancies which took place during the prediabetic stage, there were 16 or 20.5 per cent abortions, 4 or 5.1 per cent stillbirths, and 1 or 1.3 per cent neonatal deaths. Of the 57 (73.1 per cent) surviving infants, 2 were found to be abnormal; this amounts to 2.6 per cent of all pregnancies and to 3.5 per cent of the surviving offspring.

In the 48 normal control mothers there were 249 pregnancies (Table I). Of these, 31 or 12.4 per cent resulted in abortions, 3 or 1.2 per cent in stillbirths, and 9 or 3.6 per cent in neonatal deaths. Of the 206 (82.7 per cent) surviving offspring, only 1 is abnormal; this constitutes 0.4 per cent of all 249 pregnancies and 0.5 per cent of the surviving children.

It is clear that the differences in the percentage of abortions, stillbirths, neonatal deaths, and abnormal surviving children between the group of diabetic and matched normal control mothers are sufficiently great to indicate that real factors and not sampling error have been operating in the diabetic women to account for the excessive pregnancy wastage and the increased number of abnormal surviving offspring. In general, the unfavorable outcome of pregnancies during the prediabetic stage falls between the values obtained in diabetic and normal control groups, being 50 per cent or more lower than in diabetics. The neonatal deaths were unexpectedly low in our sample of prediabetic women.

TABLE I. THE OUTCOME OF PREGNANCIES IN THE SAMPLES OF DIABETIC, PREDIABETIC, AND NORMAL CONTROL MOTHERS

	ABORTIONS		STILLBIRTHS		NEONATAL DEATHS		ABNORMAL SURVIVING		NORMAL SURVIVING		TOTAL PREGNANCIES
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
48 Diabetics	47	29.9	18	11.5	13	8.3	6	3.8	73	46.5	157
(C 17;N 31)	(C 16;N 31)		(C 7;N 11)		(C 4;N 9)		(C 2;N 4)		(C 24;N 49)		(C 53;N 104)
48 Prediabetics	16	20.5	4	5.1	1	1.3	2	2.6	55	70.5	78
(C 17;N 31)	(C 2;N 14)		(C 1;N 3)		(C 0;N 1)		(C 0;N 2)		(C 2;N 53)		(C 5;N 73)
48 Normal controls	31	12.4	3	1.2	9	3.6	1	0.4	205	82.3	249
(C 17;N 31)	(C 8;N 23)		(C 0;N 3)		(C 0;N 9)		(C 0;N 1)		(C 58;N 147)		(C 66;N 183)

C = Caucasian.
N = Negro.

Since the total pregnancy wastage in diabetes (sum of abortions, stillbirths, and early neonatal deaths) and the incidence of abnormal surviving offspring are of a particular interest in this study, they were compared in the sample groups of diabetics and matched normal controls for statistical significance. Using the t test in statistical analysis of the differences in percentages for the pregnancy wastage between the diabetics and normal controls, it was found that the difference was significant at 1 per cent level ($t = 7.18$). Similar calculation for the differences in percentages in abnormal surviving offspring between diabetics and normal controls showed a t value significant also at the 1 per cent level.

To satisfy the reasoning that in a statistical study the patient is the sampling unit (in this instance the pregnant mother), additional evaluation is made. The outcome of the first pregnancies in the diabetic woman is compared with the outcome of that pregnancy in the normal control mother, when the latter was of approximately similar age as the diabetic woman whom she was matching. A separate comparison was made for the second pregnancy after the diagnosis of diabetes was established. The detailed data may be seen in Table II. Before comparing the outcome of gestation in diabetics and normal matched controls, it can be stated that the pregnancy wastage and the number of abnormal survivors from the first and second pregnancies after the diagnosis of diabetes were closely alike. This is also true of the respective two pregnancies in the matched normal controls. Since the number of pregnancies in diabetic and normal control mothers are identical, the numbers listed in Table II under abortions, stillbirths, neonatal deaths, and abnormal surviving offspring can be compared directly. Thus, arguing from the sample of normal population, the number of abortions in the first pregnancies of diabetics should be 6 instead of the 13 observed, the number of stillbirths should be 1 or less instead of the 6 observed. The number of neonatal deaths should not exceed 1 instead of the 4 observed, and the number of abnormal surviving offspring should be 1 or less instead of the 2 observed. Expressing the outcome of pregnancy by means of normal surviving offspring it can be stated that there should be 41 normal living children out of 48 pregnancies in diabetics instead of the 23 actually observed.

DISCUSSION

The comparison of proportions indicates that there is no basic difference in the incidence of pregnancy wastage and the incidence of abnormal survivors between the sample of first pregnancies and the sample of total pregnancies in the same diabetic women. Also, the comparison of the percentages of the pregnancy wastage in the first gestations of the diabetics and the corresponding gestations in the normal controls (see Table II) reveals striking similarity to the corresponding percentages obtained in the entire sample of the normal controls as shown in Table I. Thus, the pregnancy wastage and the incidence of abnormal surviving offspring is significantly higher in these two categories of pregnancies in diabetic women than in the respective normal controls. In view of these findings

TABLE II. THE OUTCOME OF FIRST AND SECOND PREGNANCIES IN DIABETICS CONSIDERED SEPARATELY AND THE OUTCOME OF CORRESPONDING PREGNANCIES IN NORMAL CONTROLS

	ABORTIONS		STILLBIRTHS		NEONATAL DEATHS		ABNORMAL SURVIVING		NORMAL SURVIVING		TOTAL PREGNANCIES
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Outcome of first pregnancies in diabetics	13 (C 5;N 8)	27.1	6 (C 3;N 3)	12.5	4 (C 0;N 4)	8.3	2 (C 0;N 2)	4.2	23 (C 9;N 14)	47.9	48 (C 17;N 31)
Outcome of pregnancies in controls as matched with first pregnancies in diabetics	6 (C 2;N 4)	12.5	0		1 (C 0;N 1)	2.1	0		41 (C 15;N 26)	85.4	48 (C 17;N 31)
Outcome of second pregnancies in diabetics	15 (C 7;N 8)	31.2	6 (C 0;N 6)	12.5	5 (C 4;N 1)*	10.4	2 (C 1;N 1)	4.2	20 (C 5;N 15)	41.7	48 (C 17;N 31)
Outcome of pregnancies in controls as matched with second pregnancies in diabetics	3 (C 2;N 1)	6.2	0		2 (C 0;N 2)	4.2	0		43 (C 15;N 28)	89.6	48 (C 17;N 31)

*Twins (twin A died when 1 day of age, twin B at 1 week).

we can now concentrate on the analysis of factors which might have been responsible for the increased pregnancy wastage and the higher incidence of abnormal surviving offspring in the diabetic mothers. The following conditions are considered worth investigating in detail: (1) severity of the diabetes; (2) other complications of pregnancy in addition to the diabetes; (3) state of control of the diabetes at the time of delivery; (4) type of delivery; (5) condition of the infant at the time of delivery.

1. *Severity of Diabetes.*—It may be seen in Table III that there were 25 pregnancies in the mothers with mild diabetes. Of these, 7 or 28.0 per cent resulted in abortion, 3 or 12.0 per cent in stillbirths, 1 or 4.0 per cent in neonatal deaths, 1 or 4.0 per cent constituted abnormal surviving offspring, and 13 or 52.0 per cent were normal surviving offspring. Of 81 pregnancies in the women with a moderate degree of diabetes, 23 or 28.4 per cent resulted in abortion, 8 or 9.9 per cent in stillbirths, 9 or 11.1 per cent in neonatal deaths, 4 or 4.9 per cent in abnormal surviving offspring, and 37 or 45.7 per cent in normal surviving offspring. Of 51 pregnancies in the severe diabetics, 17 or 33.3 per cent resulted in abortions, 7 or 13.7 per cent in stillbirths, 3 or 5.9 per cent in neonatal deaths, 1 or 2.0 per cent in abnormal surviving offspring, and 23 or 45.1 per cent in normal surviving offspring. Comparison of the percentages in the three grades of severity of diabetes mellitus suggests that there was no basic difference in the pregnancy wastage which would be dependent on the degree of severity of the diabetes if other factors such as the control of maternal diabetes and the type of delivery were similar in all three groups. Here, we wish to stress that the severity of diabetes was estimated between gestations and it may not correlate with the state of the control at the time of pregnancy. Daily fluctations between hyper- and hypoglycemia in diabetics during pregnancy is common and this makes it extremely difficult or almost impossible to properly assess and control this factor throughout the period of gestation. After dealing with large numbers of pregnancies in diabetic women, we considered that attempts at estimating the control of diabetes throughout the course of gestation would of necessity be inaccurate.

2. *Other Complications of Pregnancy in Addition to the Diabetes.*—The influence of toxemia, polyhydramnios, hypertension, and vaginal bleeding in diabetics was analyzed in relation to the final outcome of gestation; the abortions were not considered. Toxemia of pregnancy was observed in 6 gestations but all resulting offspring were normal. Elevation of blood pressure without marked urinary abnormality was observed in 8 pregnancies; in 6 of these, normal offspring were born and 2 resulted in premature births followed by early neonatal death. Considerable vaginal bleeding prior to the delivery (in 2 from premature separation of the placenta, and in 3 of undetermined origin) occurred in 5 pregnancies; 2 of the resulting offspring died during the neonatal stage and 1 was stillborn. Marked polyhydramnios was present in 7 of 110 pregnancies. Only 2 of the resulting offspring survived and were normal, whereas 3 were stillborn, 1 died

TABLE III. THE EFFECT OF THE SEVERITY OF THE DIABETES ON THE FINAL OUTCOME OF PREGNANCIES

SEVERITY OF DIABETES	ABORTIONS		STILLBIRTHS		NEONATAL DEATHS		ABNORMAL SURVIVING		NORMAL SURVIVING		TOTAL PREGNANCIES
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Mild											
9 mothers (C 1;N 8)	7 (C 0;N 7)	28.0	3 (C 1;N 2)	12.0	1 (C 0;N 1)	4.0	1 (C 1;N 0)	4.0	13 (C 1;N 12)	52.0	25 (C 3;N 22)
Moderate											
22 mothers (C 11;N 11)	23 (C 10;N 13)	28.4	8 (C 3;N 5)	9.9	9 (C 3;N 6)	11.1	4 (C 1;N 3)	4.9	37 (C 17;N 20)	45.7	81 (C 34;N 47)
Severe											
17 mothers (C 5;N 12)	17 (C 6;N 11)	33.3	7 (C 3;N 4)	13.7	3 (C 1;N 2)	5.9	1 (C 0;N 1)	2.0	23 (C 6;N 17)	45.1	51 (C 16;N 35)
Totals	47 (C 16;N 31)		18 (C 7;N 11)		13 (C 4;N 9)		6 (C 2;N 4)		73 (C 24;N 49)		157 (1 Twin) (C 53;N 104)

during the neonatal stage, and the remaining 1 survived but is abnormal. These numbers are too small to permit statistical evaluation. However, comparison of proportions of unfavorable outcome of gestation in diabetics with the complications of pregnancy described above and diabetic pregnancies without such complications suggests that polyhydramnios and uterine bleeding prior to delivery are more frequently associated with pregnancy wastage. Toxemia of pregnancy and excessive elevation of blood pressure during gestation in our series did not worsen the prognosis for survival of normal offspring.

3. *The Effects of the Control of the Diabetes at the Time of Delivery on the Outcome of Pregnancy.*—The total incidence of stillbirths, neonatal deaths, and live abnormal offspring in the group of 63 pregnancies with satisfactory control of the diabetes at the time of delivery was 25.4 per cent; therefore, the expected number of pregnancies with unfavorable outcome in the poorly controlled diabetics at the time of delivery would be 12 instead of the 21 observed (Table IV). This may suggest that real factors and not sampling error were operating in the mothers with poorly controlled diabetes at the time of delivery to account for the difference.

4. *The Effect of the Type of Delivery in Diabetic Women on the State of Their Offspring.*—For the purpose of investigating the influence of the type of delivery on the mortality and morbidity of the offspring born to diabetic mothers (Table V), all deliveries were divided into two groups: (a) cesarean section or induction, 39 (cesarean section 30, induction 9); (b) spontaneous deliveries, 71.

In the group of 39 deliveries carried out by means of cesarean section or induction, the total incidence of stillbirths, neonatal deaths, and live abnormal offspring was 20.6 per cent as compared to 40.8 per cent in the group of spontaneous deliveries. This difference suggests that the outcome of gestation was more satisfactory when the delivery took place 2 to 4 weeks before term by means of cesarean section or following induction.

5. *The Condition of the Infant at Delivery as Related to His Future Well-Being.*—The total of 157 pregnancies in diabetic mothers resulted in 92 live-born infants. Of these, asphyxia was observed in 25 or 27.2 per cent (Table VI). Of the 25 infants who exhibited asphyxia at birth, 11 or 44.0 per cent died during the neonatal stage, 2 or 8.0 per cent constituted abnormal surviving offspring, and 12 or 48.0 per cent were normal surviving offspring. Since the total incidence of neonatal deaths and live abnormal offspring in the 67 infants without asphyxia at birth was 9 per cent, the expected number of neonatal deaths and live abnormal offspring taken together in infants with asphyxia at delivery would be 2 instead of the 13 observed. However, in interpreting the data in these two groups it is imperative to bear in mind that the state of the infant at birth and particularly asphyxia depends on a variety of factors associated with pregnancy and delivery of the diabetic mothers.

COMMENT

The total pregnancy wastage in the sample of diabetic mothers is 49.7 per

TABLE IV. THE EFFECT OF THE CONTROL OF THE DIABETES AT THE TIME OF DELIVERY ON THE OUTCOME OF PREGNANCY

CONTROL OF DIABETES AT TIME OF DELIVERY	STILLBIRTHS		NEONATAL DEATHS		ABNORMAL SURVIVING		NORMAL SURVIVING		TOTAL PREGNANCIES
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Satisfactory control	7 (C 4;N 3)	11.1	6 (C 3;N 3)	9.5	3 (C 2;N 1)	4.8	47 (C 14;N 33)	74.6	63 (C 23;N 40)
Poor control	11 (C 3;N 8)	23.4	7 (C 1;N 6)	14.9	3 (C 0;N 3)	6.4	26 (C 10;N 16)	55.3	47 (C 14;N 33)
Totals	18 (C 7;N 11)		13 (C 4;N 9)		6 (C 2;N 4)		73 (C 24;N 49)		110 (C 37;N 73)

TABLE V. THE EFFECT OF THE TYPE OF DELIVERY IN DIABETIC WOMEN ON THE STATE OF THEIR OFFSPRING

TYPE OF DELIVERY	STILLBIRTHS		NEONATAL DEATHS		ABNORMAL SURVIVING		NORMAL SURVIVING		TOTAL PREGNANCIES
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Spontaneous	15 (C 7;N 8)	21.1	9 (C 1;N 8)	12.7	5 (C 2;N 3)	7.0	42 (C 9;N 33)	59.2	71 (C 19;N 52)
Cesarean section (30) and induced (9)	3 (C 0;N 3)	7.7	4 (C 3;N 1)	10.3	1 (C 0;N 1)	2.6	31 (C 15;N 16)	79.5	39 (C 18;N 21)
Totals	18 (C 7;N 11)		13 (C 4;N 9)		6 (C 2;N 4)		73 (C 24;N 49)		110 (C 37;N 73)

TABLE VI. THE EFFECT OF ASPHYXIA AT BIRTH ON THE SUBSEQUENT FATE OF OFFSPRING BORN TO DIABETIC MOTHERS

STATE OF INFANT AT TIME OF DELIVERY	NEONATAL DEATHS		ABNORMAL SURVIVING		NORMAL SURVIVING		TOTAL PREGNANCIES
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Asphyxia present	11 (C 2;N 9)	44.0	2 (C 0;N 2)	8.0	12 (C 6;N 6)	48.0	25 (C 8;N 17)
Normal	2 (C 2;N 0)	3.0	4 (C 2;N 2)	6.0	61 (C 18;N 43)	91.0	67 (C 22;N 45)
Totals	13 (C 4;N 9)		6 (C 2;N 4)		73 (C 24;N 49)		92 (C 30;N 62)

cent, which is almost 3 times higher than in the sample of normal matched controls in whom it amounts to only 17.2 per cent. The total wastage of pregnancy during the prediabetic stage is 26.9 per cent, which is higher than in the normal controls but much lower than in the diabetics. The number of abnormal surviving offspring in all three categories considered is relatively small, but the comparison of percentages reveals that the incidence in offspring of diabetic mothers is about 8 times higher than that in the normal control sample. Thus, 3.8 per cent of abnormal surviving offspring were born to the diabetic mothers, 2.6 per cent born during the prediabetic stage, and 0.4 per cent in the sample of normal controls. Our hypothesis, then, that the incidence of morbidity dating since birth is higher among the children born to diabetic mothers appears to be correct. Tests for statistical significance which were calculated for pregnancy wastage and abnormal surviving offspring in the diabetic and normal control groups showed a statistical difference at $P < 0.01$.

It is interesting to compare the results obtained in pregnancy wastage in our sample with those obtained by other investigators. However, this is not an easy task as the criteria for classification of abortions, stillbirths, and even neonatal deaths vary greatly; also, certain investigators did not consider miscarriages at all. Miller and co-workers[6] (1944) and Miller[7] (1946) found the combined incidence of fetal and neonatal deaths among 93 deliveries in the diabetic mothers to be 23.6 per cent and among 252 births in prediabetic women to be 19.8 per cent. In their normal control sample the combined incidence of fetal and neonatal deaths was 5.4 per cent. However, they did not state from what gestational age "fetal deaths" were included, presumably they meant only stillbirths. Also, by definition they limited the neonatal period to the first 10 days of life. If these differences in methods are accounted for, the rates of perinatal mortality in diabetics and normal controls are not greatly different from ours. However, the pregnancy wastage in our sample of prediabetics was markedly lower than in Miller's series. Clayton[1] (1956) investigated 198 single deliveries in diabetics, two thirds of whom had cesarean sections and in the majority of the remainder, birth was induced. The combined incidence of stillbirths and neonatal deaths from his data was calculated and it amounted to 28.7 per cent. This high mortality rate was somewhat surprising, as in our sample the number of cesarean sections and induced pregnancies was about one third of the total deliveries and yet the percentage of combined stillbirths and neonatal deaths was only 19.7 per cent. When the present article was completed, Gellis and Hsia[4] (1959) published their paper on over 900 diabetic pregnancies. The total fetal wastage in their series amounted to 35 per cent as compared to 49.7 per cent in our study. This difference is largely the result of a higher rate of abortions and previable deaths in our series. They concluded from analyzing the reports of other investigators as well as their own data that there is little evidence to suggest a significant decrease in the fetal mortality in recent years. Similarly, as other authors, they stressed the fact that hyaline

membrane disease of the lungs is the largest single factor responsible for early neonatal deaths.

To our knowledge, no controlled study of morbidity among the surviving offspring of diabetic mothers was made so that our rate of 3.8 per cent of abnormal surviving offspring could not be compared directly.

In search for the factors which may be responsible for or contributing to the increased fetal loss and morbidity in the offspring of diabetic mothers, various aspects pertaining to pregnancy were analyzed. It is evident from Table III that the greater severity of maternal diabetes between the pregnancies was not associated with a higher incidence of unfavorable outcome of pregnancy if other conditions were the same. On the other hand, the presence of certain complications of pregnancy in addition to diabetes tends to increase the incidence of mortality and morbidity. Thus, polyhydramnios and uterine bleeding were associated with a higher occurrence of stillbirths, neonatal deaths, and abnormal surviving offspring, although the numbers are too small for the formulation of a definite opinion. Polyhydramnios appears to be more common in women suffering from renal disease and also in diabetics.

Poor control of diabetes at the time of delivery was associated with a significantly higher incidence of stillbirths, neonatal deaths, and abnormal surviving infants than was the case when the control of diabetes about the time of delivery was satisfactory. It is probable that the metabolic disturbance adds considerably to the risks of delivery of infants of diabetic mothers; these infants are frequently oversized. During the last stage of pregnancy there is an increased tendency to acidosis. Our unpublished data indicate that 36 hour fasting will produce marked acidosis during the last stage of pregnancy in rats, whereas during the first three fourths of gestation the level of ketone bodies on a similar regimen is normal or only slightly elevated.

Since the numbers of stillbirths, neonatal deaths, and abnormal surviving offspring among those delivered by cesarean section or by induction are small, these three categories are combined together for the purpose of direct comparison with the results obtained in infants born by spontaneous delivery. It appears that cesarean section and induced delivery at about 36 weeks of gestation lessened the incidence of stillbirths, neonatal deaths, and abnormal surviving infants as compared to the outcome of spontaneous delivery. Thus, the percentage of normal surviving offspring delivered by cesarean sections was 79.5 as compared to 59.2 among those born by spontaneous delivery. In evaluating these results, the following factor has to be considered: the diabetic women who were delivered by cesarean section or induction were admitted to the hospital a few days prior to the delivery and their diabetes was on the whole better controlled at the time of delivery than in the mothers who gave spontaneous birth. Consequently, we cannot exclude this factor as contributing to the better results in the group born by cesarean section or by induced delivery.

The incidence of neonatal deaths and abnormal surviving infants whenever asphyxia was present at birth

was greatly higher than in those infants who appeared normal at delivery. However, asphyxia of the newborn infant depends on many maternal factors preceding the delivery or acting at birth as well as on the state of the infant prior to the delivery, as for example, on the presence of serious congenital malformations. Therefore, no conclusions can be drawn from direct comparison of these two groups of infants in regard to the causation. Nevertheless, an important practical aspect needs to be stressed. Asphyxia of the infant born to a diabetic mother should be anticipated, special equipment for resuscitation kept ready, and an anesthesiologist alerted.

From these considerations, it would appear that there is more than one factor responsible for the increased pregnancy wastage and higher rate of abnormal surviving offspring born to the diabetic mothers as compared with the normal controls. The statistical study can merely indicate that certain factors are more likely to be involved than others; it may also suggest a fruitful lead for experimental investigation. Good control of maternal diabetes, particularly preceding the delivery, is very important in improving the favorable outcome of pregnancies. Complication of gestation in a diabetic by polyhydramnios is quite common and adds considerably to the risk of an unfavorable outcome of pregnancy. The infants of diabetic mothers have a greater tendency to suffer from asphyxia at birth and this fact should be anticipated and appropriate measures taken before, during, and after delivery. The question of advisability of cesarean section 2 to 4 weeks before term is complex and requires further study. Although the incidence of stillbirths with this method of delivery is decreased, the danger of these infants developing hyaline membrane disease of the lungs is quite considerable and it may offset the advantages of nontraumatic, controlled birth. Certainly, the results obtained by Clayton[1] (1956) are discouraging, as in his series the neonatal mortality from hyaline pulmonary disease in infants delivered by cesarean section amounted to 13 per cent as compared with 11 per cent of infants delivered vaginally following induction or by spontaneous delivery.

The present study has confirmed the correctness of our hypothesis that the incidence of abnormal surviving offspring born to diabetic mothers is increased as compared to the normal control population. The main abnormalities consist of congenital malformation, retardation of development, and epilepsy. We were also able to confirm the findings of previous investigations that the pregnancy wastage in the diabetic mothers is considerably higher than in the general population.

SUMMARY

The outcome of 235 pregnancies in diabetic and prediabetic women was investigated and the results obtained were compared with the corresponding data in the 249 pregnancies of matched normal controls.

The percentage of abortions and previable deaths in the diabetic sample was 29.9, in the prediabetic sample 20.5, and in the normal controls 12.4.

Stillbirths occurred with the following frequency: 11.5 per cent in the sample of diabetic mothers, 5.1 per cent in the prediabetics, and 1.2 per cent in the normal controls.

The neonatal deaths amounted to 8.3 per cent of all pregnancies in the diabetic women, 1.3 per cent in the prediabetics, and 3.6 per cent in the sample of normal controls.

These values demonstrate clearly that the fetal wastage in the diabetic women was significantly greater than in the normal controls. The fetal loss during the prediabetic stage was about midway between that in diabetic and normal control mothers. The results obtained generally confirm the findings of other investigators.

The main purpose of our study was to test the hypothesis that the morbidity dating since birth in the offspring of diabetic mothers is also increased as compared with the sample of normal controls. There were 6 abnormal surviving offspring in the sample of 157 diabetic pregnancies, which amounts to a total of 3.8 per cent (or 7.6 per cent of the surviving children). In the normal control sample of 249 pregnancies there was only 1 abnormal surviving offspring, which constitutes the incidence of 0.4 per cent. The difference in percentages in these two groups was significant at P less than 0.01, indicating that our hypothesis is very likely correct. The abnormalities in these children include mental deficiency, congenital malformations, birth injury, and epilepsy.

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A NOTE ON THE DEVELOPMENT OF GAUCHER CELLS IN A NEWBORN INFANT

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GAUCHER'S disease has two clinical variants—the acute "infantile" and the chronic "adult" forms of the disease. The infantile, a condition far less common than the adult form, customarily runs a rapidly fatal course dominated by neurologic signs. Although accumulations of Gaucher cells may be associated with pulmonary infiltration and enlargement of the spleen and liver, direct involvement of the brain with specific "storage" cells is not usually seen.[1, 2] The typical Gaucher cell, which is characteristically found in the spleen, liver, bone marrow, and lymph nodes of the adult patient, is more widespread in the infantile form of the disease. In both forms it is characterized by abundant, distinctively fibrillary cytoplasm, in which the glycolipid kerasin or its glucose analogue appears to be bound to a protein complex.[3]

In a recently studied case, signs and hematologic abnormalities referable to Gaucher's disease were observed during the first 3 days of life; although the "storage" cells were cytologically atypical, they presented the uncommon opportunity to observe the cellular changes in the earliest stages of the disease.

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CASE REPORT

C. D. was born after a normal, full-term pregnancy, and she weighed 6 pounds, 5½ ounces at birth. Both parents were Jewish; there was no history of consanguinity. Of her 2 older siblings, one was normal; the other, then age 3, had suffered for about 1½ years from chronic Gaucher's disease, which had been diagnosed by the finding of typical cells in the bone marrow and which was associated with splenomegaly and a slight anemia. The parents were apparently healthy, but the father has since died of carcinoma of the pancreas. Histologic examination of his spleen, bone marrow, and liver was negative for Gaucher cells.

Enlargement of the liver and spleen were present at birth, and there was marked cutaneous purpura. She also had several stigmas of Mongolism, including epicanthal folds, brachycephaly, spade-shaped hands, and separation of her first and second toes. The Coombs test was negative, and examination of the peripheral blood showed diminished platelets and 108 nucleated red cells per 100 white blood cells. At 3 days of age she developed vomiting and bloody diarrhea and was transferred to the Children's Hospital of Michigan.

The hemoglobin level was initially 17.4, and following dehydration it stabilized at approximately 19 Gm. per 100 ml. in association with a red blood cell count of approximately 6.5 million per cubic millimeter. The white blood cell count was, on admission, 18,150 (uncorrected for nucleated red cells), and 4 days later it was 7,000 per cubic

millimeter. The differential white cell count on the latter occasion was 55 per cent neutrophils, 40 per cent lymphocytes, 2 per cent monocytes, and 3 per cent eosinophils, and there were 7 nucleated red cells per 100 white blood cells. The reticulocyte count was 15.4 per cent, and the platelet count was 38,250, falling to 13,400 per cubic millimeter. Examination of the bone marrow on two occasions was technically unsatisfactory. Roentgenograms of the chest, skull, and long bones were negative, and the iliac index was consistent with Mongolism.

fibrillary cytoplasm, which could be stained with the periodic acid-Schiff, Sudan black B, and Hale dialyzed iron procedures. The Schiff staining was barely affected by previous enzymatic digestion (Fig. 1), and the sudanophilia was only partially extracted with lipid solvents (Table I). The staining procedures demonstrated cytoplasmic fibrils within these cells (Fig. 2), suggesting that the stored material was actually present in that form. The amount of stainable material was variable, and scattered large cells contained little or none. Only the spleen

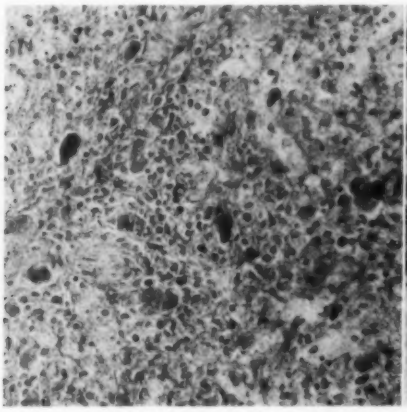

Fig. 1.

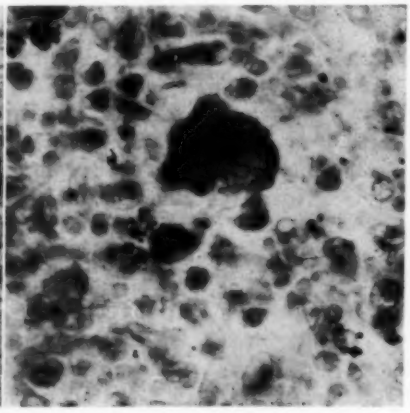

Fig. 2.

Fig. 1.—Storage cells in splenic pulp. Paraffin section. (Trypsin digestion followed by periodic acid-Schiff stain. ×210; reduced ⅙.)

Fig. 2.—Storage cell in splenic pulp containing intracytoplasmic fibrils. Frozen section. (Sudan black B stain. ×835; reduced ⅙.)

Despite negative stool cultures, she continued to suffer from diarrhea and episodes of cyanosis. Additional cutaneous petechiae appeared on the second hospital day. She was treated supportively with antibiotics and parenteral fluids, but her condition progressively deteriorated and she died after a severe cyanotic episode at the age of 14 days.

Postmortem examination disclosed abnormal large cells in the spleen which were sufficiently characteristic to warrant the diagnosis of Gaucher's disease. They contained abundant

was increased in size, weighing 19 grams (normal 11 grams), and chemical analysis of fresh-frozen tissues provided lipid levels that were within the range of normal (Table II). The liver and bone marrow contained scattered large, lightly Schiff-positive cells which resembled those seen in the spleen. Megakaryocytes could not be identified with certainty.

The only abnormalities in the brain were nerve cell heterotopia in the cerebral white matter and cerebellar cortical disruption of the sort frequently seen in Mongolism. The immediate

TABLE I. STAINING REACTIONS OF STORAGE CELLS IN THE SPLEEN

	FORMALIN/FROZEN SECTION	FORMALIN/PARAFFIN SECTION
Sudan IV	±	
Sudan black B	++++	±
Extracted with hot acetone	++++	
methanol-ether	++++	
acetone-methanol	+++	
acetone-ether	++ - +++	
Chromated	+	
Smith-Dietrich	±	
Periodic acid-Schiff	++++	+++
Extracted with cold acetone		+++
hot acetone		+++
hot acetone-ether		+++
hot ether		+++
hot pyridine		+++
Digested with diastase		++ - +++
trypsin		++ - +++
pepsin		++ - +++
testicular hyaluronidase		++ - +++
Rinehart–Abul-Haj–Hale dialyzed iron	+++	+++
Prussian blue	-	-
Schultz' Liebermann–Burchardt (cholesterol)	-	
Mallory's aniline blue		Faint blue; not typical
Phosphotungstic acid–hematoxylin		Faint blue stippling

TABLE II. ANALYSIS OF TISSUE LIPIDS*

	LIVER		SPLEEN	
PER CENT OF FRESH WEIGHT	PATIENT C. D.	NORMAL	PATIENT C. D.	NORMAL
Total lipids	3.92	3.0-4.5	3.30	2.0-3.5
Phospholipids	2.42	1.5-2.5	1.76	1.0-2.0
(% of total lipids)	(62)		(53)	
Sphingomyelin	0.489		0.383	
(% of total phospholipids)	(20)	(5-15)	(22)	(10-25)
Cholesterol	0.139	0.3-0.4	0.206	0.3-0.4
(% of total lipids)	(4)		(6)	
Glycolipids	0.313	0.2-0.6	0.298	0.2-0.6
(% of total lipids)	(8)		(9)	

*We are indebted to Allen C. Crocker, M.D., Children's Cancer Research Foundation, Boston, Mass., for performing the chemical determinations and providing the normal data.

anatomic cause of death was a relatively severe bronchopneumonia; the heart was normal.

DISCUSSION

The histologically positive periodic acid-Schiff, Sudan black B, and Hale dialyzed iron stains are consistent with the presence in the abnormal cells of a glycolipid bound to protein. The partial dissociation of Sudan and Schiff staining in the paraffin sections is in accord with Diezel's observations[4] that a lipid—possibly the "polycerebroside" described by Uzman[5]—is present in addition to the Gaucher lipoprotein.[3] Craig's observations[6] on the Hale procedure have also indicated that another extractable lipid is present, in his case blocking or masking the stain in frozen sections. The apparent contradiction between Craig's and our observations indicates that the other

lipid(s) may accumulate with time. Uzman[5] has implied that "polycerebroside" concentration seems to decrease with age, but he has also indicated that acid phosphatides may be secondarily bound by the Gaucher lipoprotein. By chemical analysis, Thannhauser and his associates[7] have shown a unique elevation of total cholesterol and of lecithin in the spleen of an 8-year-old boy with Gaucher's disease. Our observations do not clarify the nature of this other lipid, but it is apparent that substances other than glucosido- and galactosido-cerebrosides may accumulate in individual cells. If the former can displace as well as mask the Gaucher lipoprotein, the occasional loss of Schiff staining after paraffin embedding[8] is understandable.

The observations suggest that abnormal cells make their appearance before the storage of glycolipid takes place. Histologic examination of the spleen indicated that some large cells were only partially filled with stainable material and that the latter took the form of intracytoplasmic fibrils. Apparently the accumulation and packing of fibrils in the cytoplasm leads to the characteristically wrinkled or fibrillary appearance of the Gaucher cell. Thannhauser and co-workers[7, 8] have offered evidence that the disturbance in lipid metabolism leading to the storage of cerebrosides in Gaucher cells is limited to these cells, which are presumably reticular in origin, and that elevated serum cerebroside levels or other signs of a more generalized disturbance in lipid metabolism are lacking.

The normal levels of glycolipids in the spleen and liver of this case probably represent an insufficient quantity of material rather than evidence of another pathologic process, but a loss of water-soluble material during the chemical extraction process cannot be excluded.[10] It is not within the scope of this report to debate the essential differences between the acute infantile and the chronic juvenile or adult forms, but for purposes of classification this case should probably be regarded as an example of the chronic form of Gaucher's disease in a very young child —one in which thrombocytopenia, one of the usually relatively late hematologic manifestations, appeared within a few days of birth.

SUMMARY

The newborn sibling of a child known to have Gaucher's disease had, in addition to the stigmas of Mongolism, clinical enlargement of the liver and spleen and thrombocytopenic purpura. The spleen, at postmortem examination, contained cells which justified the diagnosis of Gaucher's disease. The case is regarded as an example of the chronic form of the disease, although present in its very early stages. The histologic observations suggest that the accumulated intracellular material was present as cytoplasmic fibrils, thereby accounting for the characteristic fibrillary appearance of Gaucher cells, and that cellular abnormality preceded the accumulation of lipid in the pathogenesis of the disease.

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A SPECIFIC ELECTROENCEPHALOGRAPHIC CORRELATE OF CONVULSIVE EQUIVALENT DISORDERS IN CHILDREN

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IN 1951, Gibbs and Gibbs[1] described a new type of electroencephalographic pattern which they called "14 and 6 per second positive spikes." They considered this pattern to be an abnormal finding and reported a high incidence in patients with "seizures preceded by emotional or vegetative auras" and in a significant number of patients having no convulsive seizures but recurrent attacks of pain or autonomic disturbances. This electrographic pattern as described by the Gibbses has not had wide acceptance among electroencephalographers as an abnormality, and it has been variously suggested that it is a rectification artifact or a normal characteristic of sleep. However, Kellaway and co-workers[2] have shown that this pattern is a recurrent electrographic phenomenon with distinct, specific, and consistent characteristics and that it has a low incidence in selected normal controls.

The electrical characteristics of this phenomenon and its physical parameters have been reported elsewhere.[3] Essentially, it consists of a series of sharp transients or spikes, with a predominant "positive" phase occurring in short runs of 13 to 15 spikes per second or 5 to 6 spikes per second. These discharges usually occur in the light stages of sleep and particularly in the period of transition from the hypnagogic to the true sleep state. Commonly, bursts of both 14 and 6 per second spikes may be seen in a single record on the same patient but it is not uncommon for either frequency to occur alone. The discharge is not restricted to a circumscribed focus, but it is always maximum in the posterior temporal region on one or both sides.

Thus defined, this pattern was found to occur in 2.3 per cent of a control group of 1,000 "normal" children. These children had no neurologic or other disease; however, at the time they were studied, no effort was made to screen them for the type of symptoms we later found to be common in patients with 14 and 6 per second positive spikes.

In an attempt to determine whether this electrographic pattern has any particular clinical correlations, we first studied a group of 200 children* se-

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*Children were selected because we have a normal control group of significant size only from birth to 16 years of age.

lected only on the basis of the fact that they showed the 14 and 6 per second spike pattern in their electroencephalograms.[2] It was immediately evident that a large number of these patients had been referred for one or more of three particular types of complaint. These were in order of incidence: (1) attacks of headache or abdominal pain with various other associated autonomic disturbances such as pallor, sweating, temperature variations, etc.; (2) behavioral disturbances; and (3) seizures (attacks of simple unconsciousness or generalized convulsions).

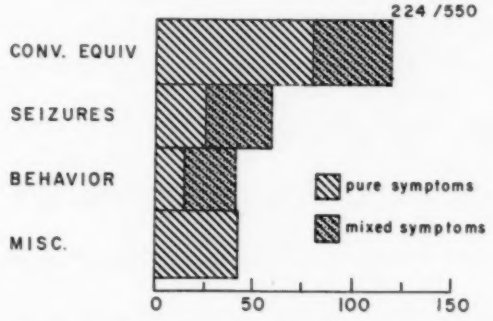

Fig. 1.—An analysis of the 241 patients whose electroencephalograms showed only 14 and 6 per second positive spikes (Group 1). The dotted areas represent cases in which a mixture of 2 or more of the 3 types of clinical abnormality were present. Note the high incidence of convulsive equivalent symptoms.

Since the original report, we have collected 450 more cases and, of the total, 550 have been adequately studied and are presented here. As in the original group, more than 50 per cent of children showing this electrographic pattern are subject to paroxysmal attacks of headache and/or abdominal pain or similar autonomic disturbances.

SUBSTANTIATION OF THE SPECIFIC RELATIONSHIP OF THE 14 AND 6 PER SECOND POSITIVE SPIKE PATTERN WITH CONVULSIVE EQUIVALENT DISORDERS

In order to evaluate the significance of any particular electrographic or clinical pattern it is necessary to obtain as pure a "culture" of the factor to be tested as possible. Thus, in this case, we should evaluate first those cases in which the 14 and 6 per second positive spike pattern was the sole electrographic abnormality. In the series of 550 patients showing positive spikes being reported here, there were 241 such children.

Fig. 1 is a graphic analysis of the 241 patients whose electroencephalograms were normal except for the presence of the 14 and 6 per second positive pattern. Of these, 129 (53.7 per cent) had recurrent attacks of either abdominal pain and/or headache occurring in brief episodes and sometimes accompanied by autonomic disturbances such as fever, nausea, vomiting, pallor, and sweating. The duration of these attacks was variable, but generally brief, lasting from 1 to 30 minutes. Upon recovery from an attack, the children usually felt quite well, but sometimes the attacks were followed by sleepiness and lethargy. Most of the patients previously had had extensive clinical studies which had failed to reveal evidence of systemic disease.

Of the 129 patients with headache and abdominal pain, 36 also either had epileptic seizures or were behavior problems.

In this group of patients with 14 and 6 per second positive spikes as the sole electrographic abnormality, 74 (30.7 per cent) had had attacks of more clearly epileptiform character; thus, 28 had had generalized convulsions either with or without fever and the others had had attacks of unconsciousness, but without convulsive movements. Of the 74 children who had had convulsions or loss of consciousness, almost half (31) had, in addition, attacks of headaches, abdominal pain, paroxysmal behavior abnormality, or other types of paroxysmal autonomic disturbance.

If we "contaminate" our sampling of patients by including patients who had, in addition to the 14 and 6 per second positive spikes, other moderate but nonspecific electrographic abnormality, such as too much occipital slow activity or a very pronounced or prolonged overventilation response, we find that the general clinical correlation is essentially unchanged. Indeed, the occurrence of these two nonspecific electrographic findings in records which show 14 and 6 per second positive spikes is so frequent that we have concluded that they are co-related abnormalities. In more than half of our cases the 14 and 6 per second positive spike pattern occurred in patients who also showed many slow-fused transients in the occipital leads and a marked and excessively prolonged response to overventilation.

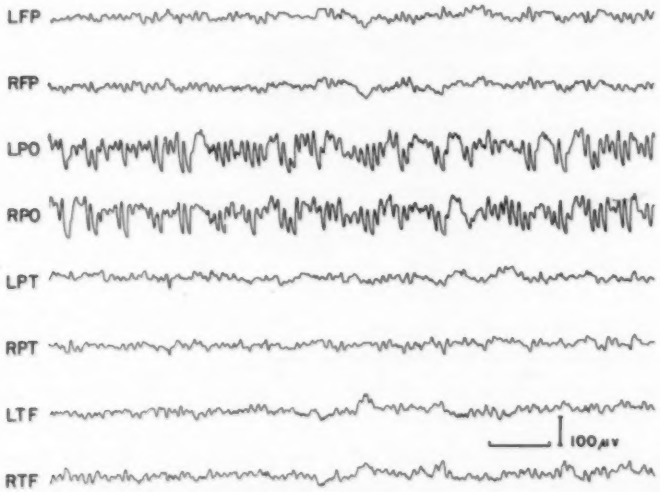

Fig. 2.—Waking electroencephalogram of Patient P. R. K., age 11 years, showing the fused waves in the occipital regions which are frequently seen in patients whose sleep records show bursts of 14 and 6 per second positive spikes.

Fig. 4 shows an analysis of the group of patients who in addition to 14 and 6 per second positive spikes showed other moderate but nonspecific (nonspecific in the sense that a focus or generalized spike and wave pattern

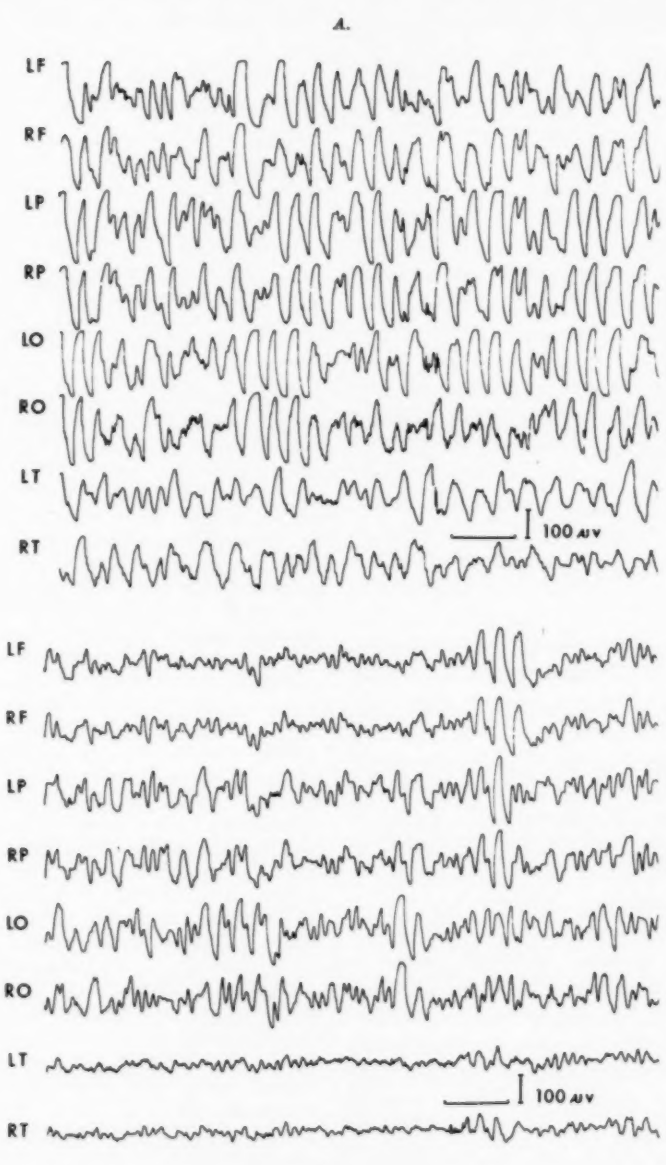

Fig. 3.—The electroencephalogram of Patient C. E. M., age 12 years, who showed a marked and prolonged overventilation response (*A*) during, and (*B*) 100 seconds after cessation of 3 minutes of overventilation. Note the high voltage generalized slow activity during overventilation and the abnormally prolonged persistence of this activity after the patient stopped overventilating.

can be considered electrographically specific) electrical abnormalities. The symptoms and their incidence in this group are not significantly different from the group with 14 and 6 per second positive spikes only. The relative incidence of attacks of pain, etc., frank seizures, and behavioral abnormalities are not statistically different in the two groups. The most important finding in terms of the question of whether or not the 14 and 6 per second positive spike pattern is an abnormality is the relatively low incidence in these two groups of patients who had *no* symptoms of this particular type. Many of these patients were children who were being studied serially following head injury or encephalitis; the 14 and 6 per second positive spike pattern generally appeared following the subsidence of the acute diffuse electrographic abnormality, the pattern apparently developing as a residual of the cerebral insult. The question of whether these children may develop the clinical symptoms associated with the presence of 14 and 6 per second positive spikes is not yet answered for all patients, but many of them have been seen to develop the typical attacks.

Fig. 5 shows what happens if the patient sample includes cases in which the electroencephalograms also revealed discharging focal abnormalities. In this group also, there was a relatively high incidence of autonomic and pain disturbances, but, as might be expected, the frequency of convulsive seizures was greater than in either Group 1 or Group 2.

If paroxysmal generalized spike and wave patterns are present in addition to 14 and 6 per second positive spikes, the incidence of frank convulsions or episodes of unconsciousness is very high (73 per cent); however, significant numbers of these children (33 per cent) also have attacks of pain, autonomic disturbance, or behavioral abnormalities.

CASE REPORTS

1. *Pain and Autonomic Disturbances.*—A typical example of the cases with so-called convulsive equivalent symptoms is Patient F. H., age 7 years, 8 months.

This patient was referred for electroencephalography because of a 2 year history of attacks of abdominal pain which were not related to meals, exercise, or any other particular factor. Each of these attacks lasted 10 to 20 minutes. The severity of the pain waxed and waned during this period. The pain was sharply localized in the center of the abdomen and did not radiate. The attacks occurred only while the patient was awake. Initially, the attacks occurred every 3 to 4 months but later began to occur as often as 3 to 5 times a week. Each attack developed and subsided rapidly. Sometimes the child vomited once or twice at the height of the attack. The vomiting was immediately preceded by pallor and occasionally a temperature elevation to 103° or 104° F. The temperature elevation, pallor, and vomiting subsided when the abdominal pain stopped. No aura or premonitory symptoms and no postictal abnormalities were noted. The past history was unremarkable. The child was of normal intelligence, was in the third grade in school, and was doing well. She did not present a behavior problem. The only significant family history was that a paternal grandfather had had epilepsy. The physical examination was within normal limits. The waking EEG was poorly organized and moderately slow for the child's age. During light sleep repeated bursts of 14 and 6 per second positive spikes were recorded.

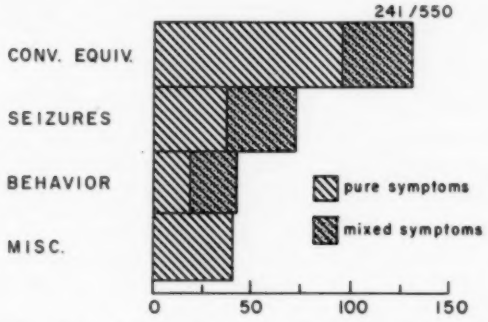

Fig. 4.—An analysis of the 224 patients whose electroencephalograms showed nonspecific abnormalities in addition to 14 and 6 per second positive spikes (Group 2). The dotted areas again represent patients who had more than one type of symptom. The statistical distribution of symptoms does not vary significantly from the group of patients in whom 14 and 6 per second positive spikes were present in "pure culture." The high incidence of convulsive equivalent attacks is again striking.

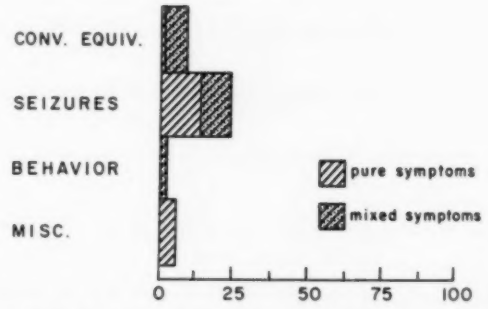

Fig. 5.—An analysis of the patients whose electroencephalograms showed focal discharges in addition to 14 and 6 per second positive spikes (Group 3). Note the increased incidence of seizures, but the incidence of convulsive equivalents remains essentially the same.

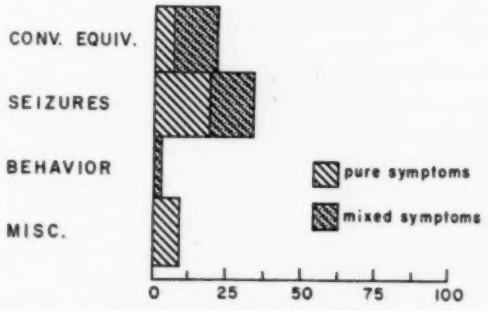

Fig. 6.—An analysis of the patients whose electroencephalograms showed both spike and wave bursts and 14 and 6 per second positive spikes (Group 4). The highest incidence of convulsive seizures and/or episodes of unconsciousness occurred in this group.

2. *Behavioral Disturbances.*—Although the number of patients in this series showing behavioral disturbances is not statistically impressive, individually this group is interesting because of a close correlation between the presence of 14 and 6 per second positive spikes and a clinical history of episodes of aggressive and destructive behavior. This has been noted by other workers.[4-6]

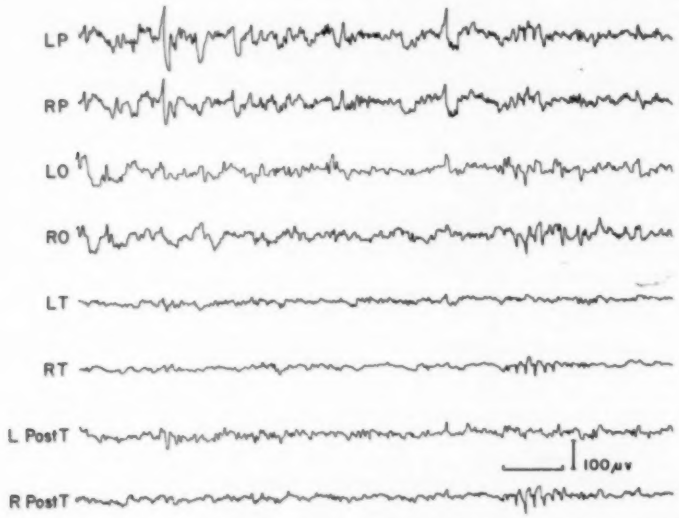

Fig. 7.—A sample, demonstrating the 14 and 6 per second positive spike pattern (in this sample occurring in 6 per second bursts), taken from the sleep electroencephalogram of Patient F. H., age 7 years, 7 months, who was studied because of attacks of abdominal pain.

A characteristic example of the type of clinical picture seen in the behavioral disorders associated with 14 and 6 per second positive spikes is Patient R. R., age 10 years, 11 months.

This boy was referred for electroencephalography because of behavioral abnormalities which had been evident since the age of about 7 years. These occurred episodically, and at other times the patient was an agreeable and easily managed child. The episodes of behavioral disturbances were generally of a destructive nature. On one occasion he set fire to his grandmother's garage; on another occasion he broke into a neighbor's home through the window, broke their radio into small pieces, and threw mud around the house. This outburst was quite unprovoked and apparently occurred without specific malice. He occasionally broke windowpanes and screen doors for no apparent reason. He occasionally killed animals. When he was questioned as to reasons for committing these acts, his only response was to shrug and say that he didn't know why he did it. Various kinds of punishment were administered such as physical chastisement, deprivation of pleasures, pocket money, and so on, but all proved ineffective. Twice during the past year he had had "fainting spells"; the first occurred when he was being questioned by his father about an episode in which he attempted to tear down the wall around the back of the house. He suddenly fell backward, his eyes rolled up, and his face was pale. He was unresponsive for about 20 seconds. At first he was rigid, then

flaccid. He was picked up and put in bed and appeared to be quite normal in 2 or 3 minutes. The second "fainting spell" also occurred when he was being reprimanded by his father and it was essentially similar to the first one. The child occasionally complained of severe "stomach-ache" and vomiting during or immediately following one of his episodes of destructive behavior.

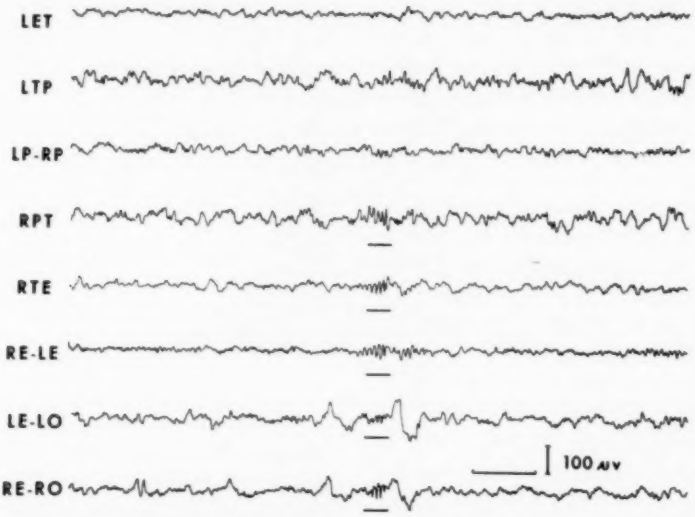

Fig. 8.—Bursts of positive spikes (in this sample occurring in 14 per second bursts) were present in the sleep electroencephalogram of Patient R. R., who had attacks of sudden destructive behavior.

The past history was unremarkable except that the child's head had had severe bruises following delivery. The family history and other personal history were not remarkable. The physical and neurologic examination revealed no evidence of abnormality. The EEG showed episodes of 14 and 6 per second positive spikes in sleep. The waking record was normal.

This case is an example of those which are classified in Figs. 1, 3, 4, and 5 as belonging in the "mixed" group, in that the child had attacks of unconsciousness in addition to episodic destructive behavior.

ETIOLOGY

In the majority of the patients included in this study it was not possible to implicate a specific etiological cause for the abnormality. Head injury (115 patients or 20.9 per cent) and encephalitis (97 patients or 17.7 per cent) were the most commonly occurring antecedent factors in the history which could be implicated as the causative agent. Some of the patients (21 patients or 3.8 per cent) who were included in this study and who had no ictal or equivalent symptoms at the time the electroencephalograms were made were children who were being followed serially following a head injury or encephalitis as has been noted above. These children developed 14 and 6 per second positive spikes usually after the resolution of the initial diffuse abnormality. Prolonged follow-up studies in most of the children in this group demonstrated that

the majority of patients showing 14 and 6 per second positive spikes after an injury or illness of this type eventually develop the clinical syndrome with which this pattern appears to be associated.

The evidence indicates that the cerebral insult which produces the EEG abnormality and the associated symptoms may sometimes be a subtle one. This is suggested by our experience of seeing the electroclinical pattern develop in children following a minor head injury or an exanthematous disease in which there was no clinically apparent encephalitic involvement. In such cases, however, the clinical records of the illness often revealed that the exanthematous disease was somewhat unusual in its course in that there were uncommonly high or prolonged bouts of fever, unusual irritability, or lethargy, etc.

Heredity certainly does not appear to be a significant etiological factor. In these 550 patients, less than 2 per cent had a family history of any kind of disorder of the nervous system.

INCIDENCE

The 14 and 6 per second positive spike pattern is much more common in children than it is in adults. The pattern appeared in 10.2 per cent of all children referred to our laboratories for study because of symptoms referable to the central nervous system. In striking contrast to this is the incidence of 0.53 per cent in a series of 14,000 adult patients. The explanation of this marked difference in incidence is unknown but it is suggested, on the basis of ontogenetic studies,[7] that the age at which a cerebral insult is incurred is a significant factor in determining the character of the electrographic and probably the clinical abnormality which results.

Long-term follow-up (up to 7 years) of patients in this group have shown that the general trend or tendency is for the EEG abnormality and the clinical symptoms to disappear with increasing age. This would account for the shape of the age incidence curve and is the basis for the clinical fact that paroxysmal abdominal pain and headache of this type are comparatively rare in adults.

Fig. 9 shows the distribution of the abnormality in the various age groups. It is relatively rare before the age of 4 to 6 years. The peak of incidence is between 4½ and 13½ years of age, with a sharp maximum at 9 to 10 years. The drop in incidence is fairly rapid thereafter.

PROGNOSIS

The length of time during which any one child will show positive spikes is, of course, highly variable; but it has been our experience that the abnormality tends to disappear within 1 to 2 years regardless of the age at which it is first seen. Exceptions to this occur and we have seen patients who showed positive spikes for as long as 7 years.

As has been reported by others,[8] the symptoms associated with positive spikes are frequently relieved or improved by anticonvulsant drugs. The patients who showed the best response to anticonvulsants are those whose attacks are paroxysmal in nature. Children who have attacks of sudden onset of headache, abdominal pain, unexplained destructive behavior, or

episodic attacks of autonomic dysfunction (fever, pallor, sweating, etc.) usually are improved with such treatment. Clinical seizures including syncopal attacks are also amenable to anticonvulsant drug therapy. However, disorders which are of a continuous or chronic type, for example, continuous behavioral abnormality or endocrine dysfunction, rarely show good response to drug therapy.

istics of the electrical discharge and its distribution (field) at the scalp do, however, indicate a deep midline origin.[3]

Unlike the 3 per second spike and wave pattern, the 14 and 6 per second positive spike pattern does not constitute the seizure discharge itself. This is demonstrated by the fact that the patients showing this abnormality in interictal periods generally show

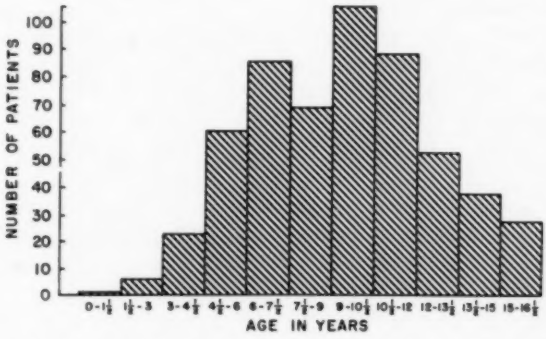

Fig. 9.—An analysis of the age incidence of children with 14 and 6 per second positive spikes.

Dilantin either alone or with phenobarbital has proved the most effective therapy in the majority of our cases.

DISCUSSION

The 14 and 6 per second positive spike pattern is believed to be electrical evidence of disordered brain function. Gibbs and Gibbs[1] suggested that the pattern is a sign of an epileptiform disturbance originating in the thalamus or hypothalamus. The Gibbses based this hypothesis almost entirely on the character of the clinical accompaniments of the electrographic abnormality and no definitive experimental work has been done which proves this discharge originates in the diencephalon. Certain character-

other types of paroxysmal activity, usually hypersynchronous slow, at the time of a clinical attack. This pattern, then, is a *sign* of disorder in a particular functional system. The underlying lesion of which the electrical abnormality is a manifestation apparently is generally epileptogenic in that it usually is associated with clinical and electrical abnormalities of paroxysmal character.

As the 14 and 6 per second positive spike pattern is not itself a seizure discharge, it cannot be expected to have a clinical correlation of the same degree of specificity that, for example, the 3 per second spike and wave pattern exhibits. The discharge must be considered more akin to a temporal

lobe spike focus, a sign of abnormal activity in a relatively large and complex neuronal system. The exact localization of the abnormally discharging area within this structure is the factor which determines the characteristics of the clinical seizure phenomena which the patient will experience. The ability of the discharge to spread and increase determines whether or not the patient will experience any paroxysmal *clinical* symptoms. The situation is essentially similar in a case of 14 and 6 per second positive spikes, the seat of the abnormality, however, being in some deep midline (diencephalic?) structure.

SUMMARY

A study of a series of 550 patients showing the electroencephalographic pattern known as 14 and 6 per second positive spikes has shown that this pattern is a particular correlate of convulsive equivalent disorders in children and provides objective laboratory evidence to support such a diagnosis. The high incidence of paroxysmal attacks of headache, abdominal pain, and behavioral and autonomic disturbances in patients with the 14 and 6 per second positive spike pattern may be considered the basis of definition for a specific electroclinical syndrome. This syndrome has its greatest incidence between the ages of 4 and 15 years but may occur at any time of life. The prognosis in children is favorable for spontaneous remission of symptoms with increasing age, and good therapeutic response to anticonvulsant drug therapy is usually the case.

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AMINOACIDURIA IN EPILEPSY

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AN INCREASED understanding of biochemistry and the development of new techniques for the study of metabolic disorders have resulted in an improved insight into the biochemical abberations responsible for or associated with disorders of the central nervous system.[1, 2, 3] Genetically determined defects in biochemical functions are associated with some disorders of central nervous system function as in phenylketonuria and hepatolenticular degeneration.[4, 5] In light of such abnormalities we have studied the patterns of the amino acids in the serum and urine of patients with a variety of convulsive disorders.

MATERIAL AND METHODS

Determinations were made of the amino acid content of the urine and serum of children classified as having grand mal epilepsy in 5 instances, petit mal epilepsy in 2, both grand mal and petit mal in 3, and status epilepticus in 4. Two patients with encephalitis were also similarly studied. The patients were from 2 to 10 years of age. Measurements of amino acids in the urine and serum of 6 normal children of similar age served as a control. The patients were studied before seizures, during seizures, between seizures, and following successful anticonvulsive therapy when the child was free of convulsions. Three of the children selected as controls received phenobarbital, tridione, or hydantoin, respectively, to determine whether the drugs might modify aminoaciduria to some extent. No evidence was found of an effect by these drugs upon the amino acid content of either the serum or the urine.

Two-dimensional chromatography was performed by the methods of Consden, Gordon, and Martin[6] and of Dent[7, 8] with phenol-water and pyridine–amyl alcohol–water used as the solvents. Patterns were obtained with 0.05 ml. of protein-free serum and with urine containing approximately 500 gamma of nitrogen. All chromatograms of urine were performed upon an aliquot of a 24 hour collection.

RESULTS

Serum Amino Acids.—The assays of the sera from patients showed the presence of only 4 to 6 amino acids which were identical to those observed in the control group. The intensities of the Ninhydrin-stained spots were equivalent to 10 to 30 gamma of a prototype taurine solution. In addition, the amino acid nitrogen concentrations in the sera of the patients were within the normal range.

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TABLE I

INITIALS AND SEX	AGE (YEARS)	HISTORY	CHROMATOGRAM OF THE URINE				EEG
			PRIOR TO A SEIZURE	DURING A SEIZURE	FOLLOWING A SEIZURE	AFTER TREATMENT	
Patients With Grand Mal Seizures.—							
A. A. (F)	7	Generalized seizures at intervals during the last 1½ years	8 amino acids	14 amino acids	8 amino acids	6 amino acids, 10 days later	Pattern of cerebral dysrythmia; improvement one month later
P. D. (M)	4	During the past year infrequent attacks of grand mal		17 amino acids			Paroxysmal bursts of slow waves
P. P. (M)	3½	During the last 6 months several attacks of grand mal		12 amino acids	3 amino acids	6 amino acids, 3 days later	Paroxysmal slow waves
G. D. (M)	4½	During the last 5 months 2 generalized seizures	8 amino acids	13 amino acids		8 amino acids, 2 days later	Pattern of epilepsy
P. D. (F)	10	For 4 years several focal and generalized attacks	8 amino acids	16 amino acids	10 amino acids	5 amino acids, 40 days later	Slow waves and complexes of spikes and waves
Patients With Grand Mal and Petit Mal Seizures.—							
K. E. (F)	10	For 3 years infrequent attacks of grand mal and petit mal		16 amino acids	12 amino acids		Typical complexes of spikes and waves; same pattern one month later
C. G. (M)	4	For 3 years infrequent attacks of grand mal and petit mal		16 amino acids		7 amino acids, 9 days later	Complexes of spikes and waves
P. K. (F)	2	For a month, several minor attacks of petit mal per day and intermittent grand mal		14 amino acids	12 amino acids	7 amino acids, 4 days later	Typical record of epilepsy
Patients With Petit Mal Seizures.—							
A. T. (M)	4	For a year several minor attacks of petit mal	7 amino acids	7 amino acids		6 amino acids	Complexes of spikes and waves
T. P. (M)	6	During the last 2 months several attacks of petit mal per day	7 amino acids	6 amino acids		7 amino acids	Complexes of spikes and waves

Patients With Encephalitis.—							
K. D. (M)	3½	Encephalitis with generalized seizures		14 amino acids	8 amino acids	6 amino acids, 10 days later	Generalized slow waves
M. M. (M)	5½	Encephalitis with generalized seizures		13 amino acids		7 amino acids, 7 days later	Generalized slow waves; improvement one month later
Patients With Status Epilepticus.—							
P. A. (F)	6	Tuberous sclerosis; mental retardation; generalized seizures of grand mal and petit mal	8 amino acids	14 amino acids		6 amino acids, 8 days later	Generalized slow waves; same pattern 12 days later
S. V. (F)	12	For the last 3 years attacks of grand mal		13 amino acids	11 amino acids		Generalized slow waves; normal record one week later
M. M. (M)	8	Two attacks of grand mal in past 2 years; status epilepticus		7 amino acids		7 amino acids, 2 days later	Patterns of coma
M. S. (F)	9	Cerebral palsy; mental retardation		17 amino acids		Status improved; 9 amino acids	Patterns of coma

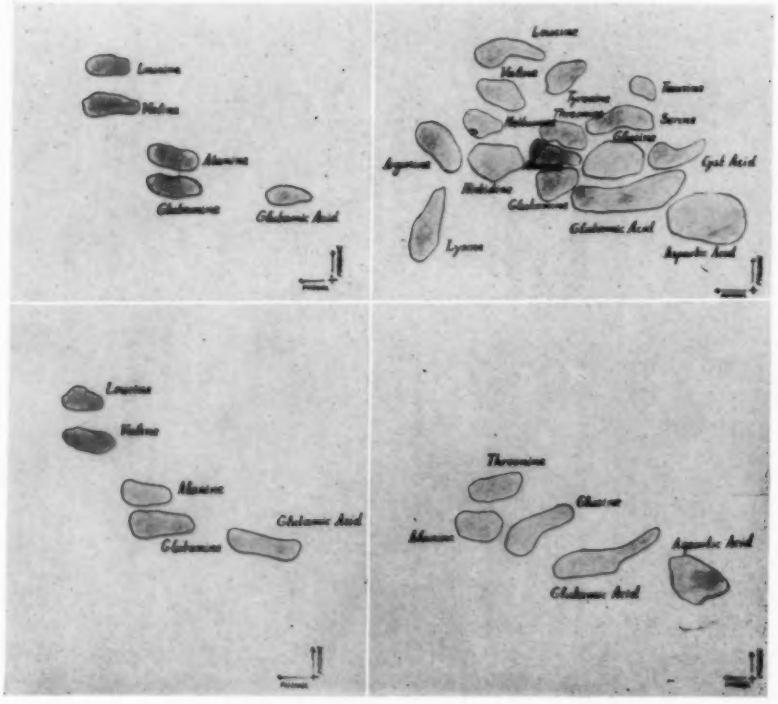

Fig. 1.—Child, 10 years of age, with grand mal epilepsy. *A*, Serum and *B*, urine chromatograms during convulsive seizure; *C*, serum and *D*, urine chromatograms 40 days later, when the patient was free of seizures.

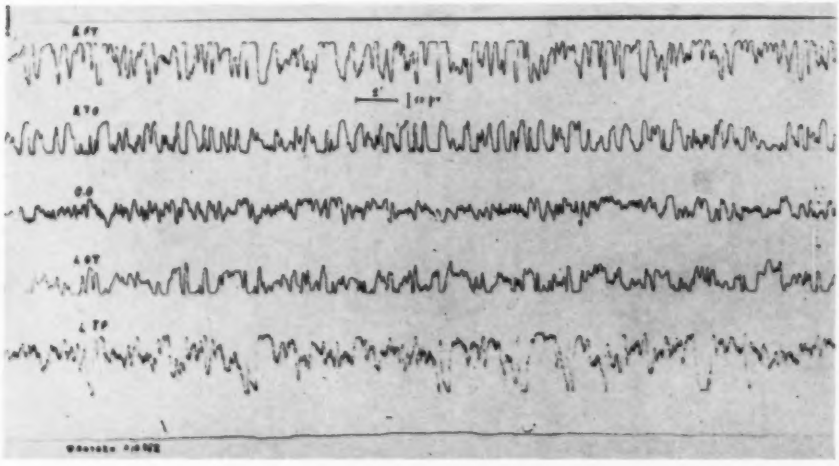

Fig. 1A.—Same case as in Fig. 1. Electroencephalogram with atypical complexes of spikes and waves and/or spikes.

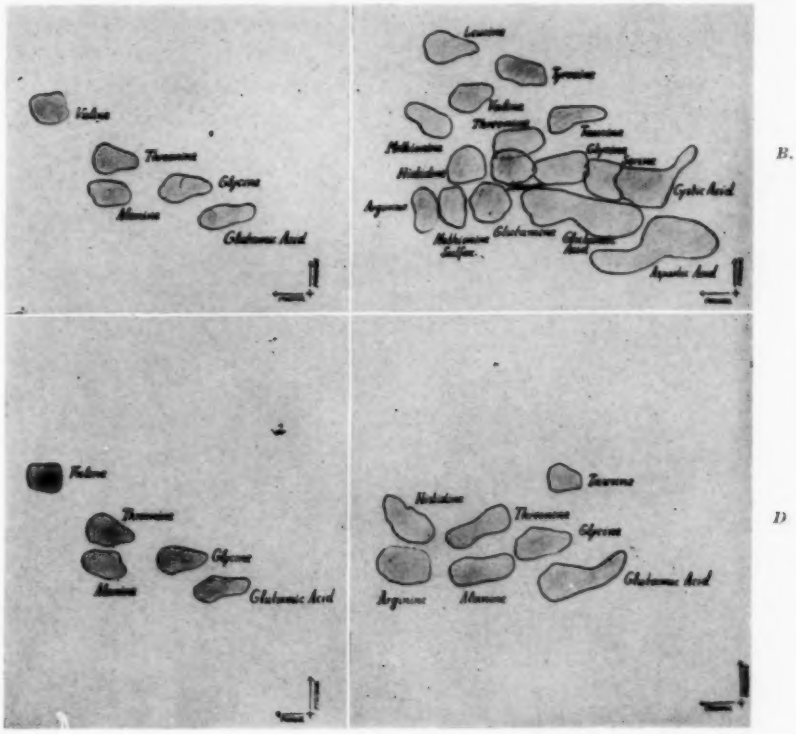

Fig. 2.—Child, 4 years of age, with grand mal and petit mal seizures. *A*, Serum and *B*, urine chromatograms during convulsive seizures; *C*, serum and *D*, urine chromatograms 9 days later, when the patient was free of seizures.

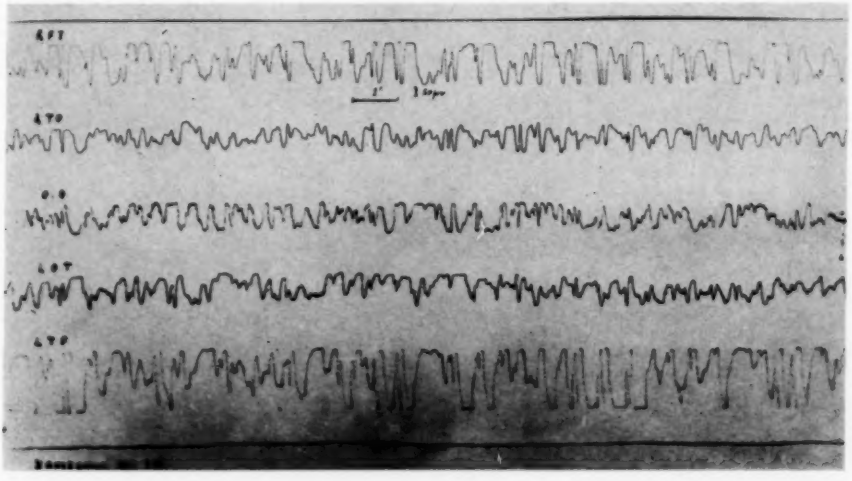

Fig. 2*A*.—Same case as in Fig. 2. Electroencephalogram with slow waves and complexes of spikes and waves.

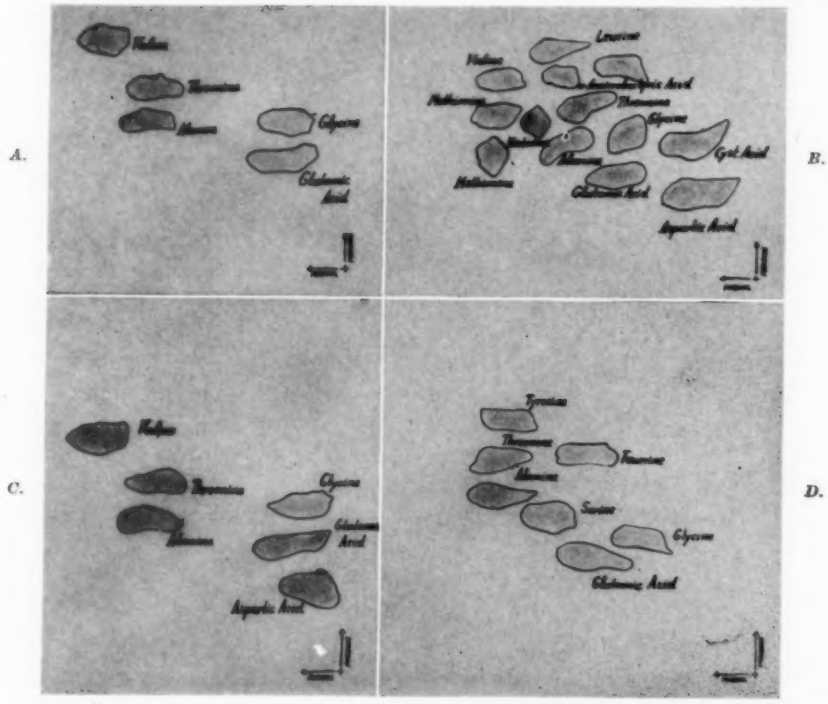

Fig. 3.—Child, 5½ years of age, with encephalitis. *A*, Serum and *B*, urine chromatograms during convulsive seizures; *C*, serum and *D*, urine chromatograms 7 days later, when the patient was free of seizures.

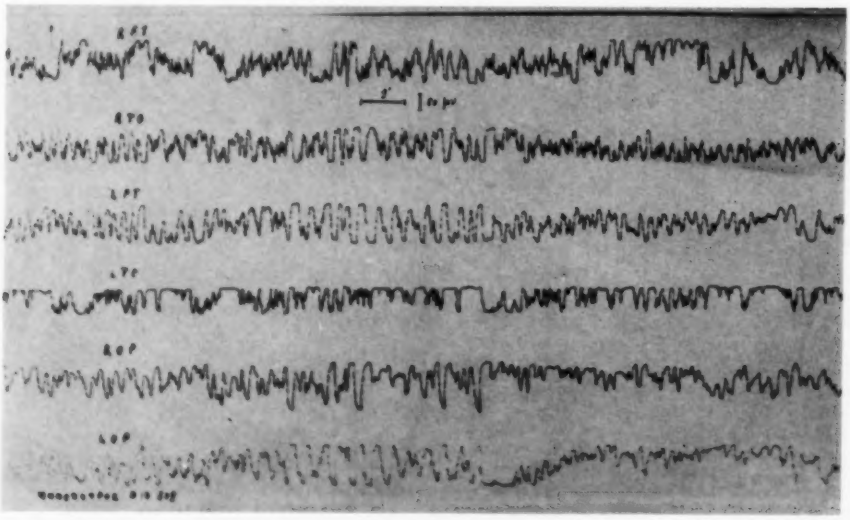

Fig. 3A.—Same case as in Fig. 3. Electroencephalogram with generalized slow waves.

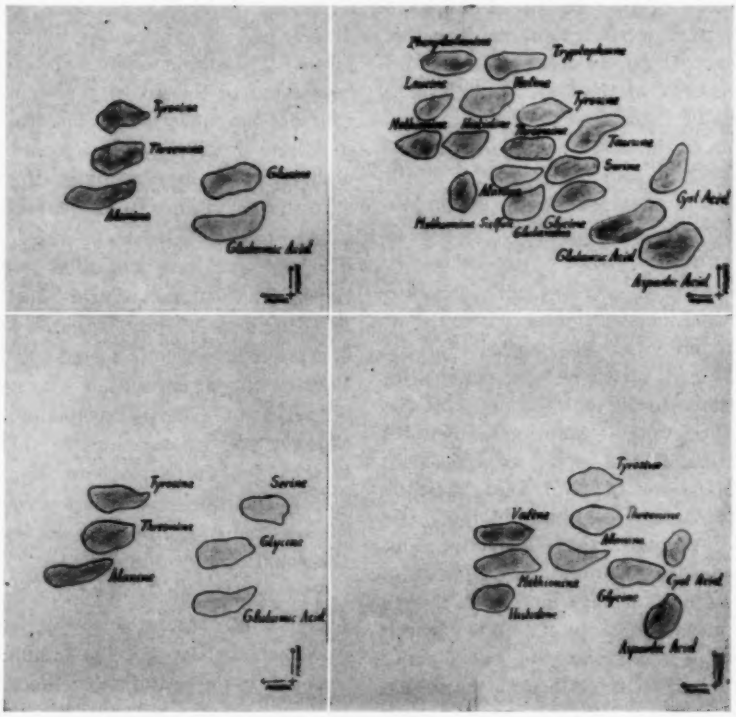

Fig. 4.—Child, 9 years of age, with status epilepticus. *A*, Serum and *B*, urine chromatograms during an episode of status epilepticus; *C*, serum and *D*, urine chromatograms after improvement.

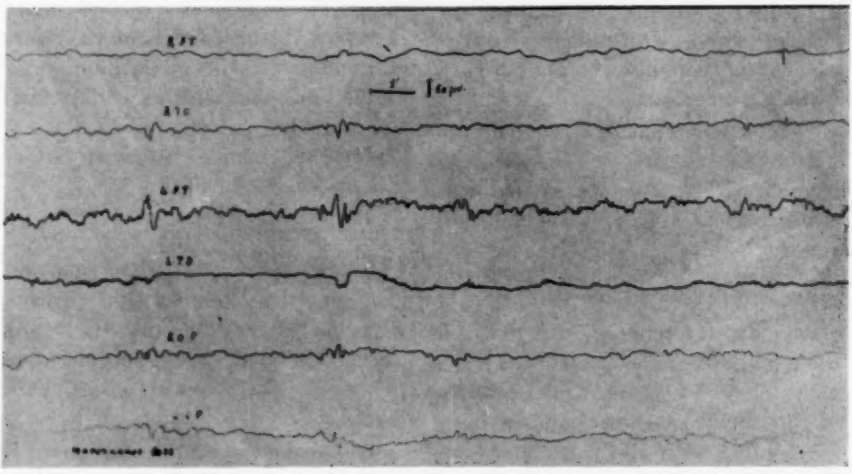

Fig. 4*A*.—Same case as in Fig. 4. Electroencephalogram with almost complete abolition of electrical activity.

Urinary Amino Acids.—Four to 6 amino acids were present in the urine of the patients between attacks and after control of the seizures with anticonvulsive therapy and thus were comparable to the observations in the children of the control group. The intensities of the spots on the chromatograms were equivalent to 10 to 30 gamma of taurine.

During the seizures an increased aminoaciduria was observed in 13 of the 16 patients. The majority of the amino acid spots showed intensities equivalent to 50 to 100 gamma of the prototype taurine solution (Figs. 1-4 and Table I). Alanine, aspartic acid, valine, glycine, glutamic acid, histidine and tyrosine were found in the urine of all 13 patients. Glutamine and threonine were found in 2 patients; methionine and cystine in 8; lysine and methionine in 3, and phenylalanine, α-aminobutyric acid and tryptophan in 2. All abnormal urine contained from 13 to 17 amino acids.

The 3 patients who had an essentially normal pattern of urinary amino acids were the 2 with only petit mal attacks and one of those with status epilepticus who was in coma but who did not have muscular contractions.

The electroencephalographic patterns were consistent with the diagnoses; the patients with encephalitis showed generalized slow waves in both hemispheres.

DISCUSSION

An abnormal aminoaciduria in which the number of amino acids in the urine appeared to be related to the severity of the convulsions was found in 13 of 16 children with epilepsy despite apparently normal concentrations of amino acids in the patients' sera as determined by chromatography technique. The aminoaciduria appeared to be related to the severity of muscular contractions since it was most evident in those patients with grand mal epilepsy and was minimal in those with petit mal and in one patient with status epilepticus who was in coma but who did not have muscular contractions. The aminoaciduria decreased as seizures were controlled and became normal when they ceased entirely. There was poor correlation between the severity of electroencephalographic changes and aminoaciduria; this was most evident in the patients with petit mal epilepsy in whom there were typical spike and wave complexes with no abnormal aminoaciduria.

The pathogenesis of the aminoaciduria is obscure. No increase in the concentration of alpha–amino acid–nitrogen in the serum was demonstrable by the chromatographic techniques used or by chemical analysis. The aminoaciduria would appear to be the result of functional renal changes. However, further studies of the clearances of amino acids by the kidney and of the effects of anoxia, urinary pH, and urinary output upon aminoaciduria are required before the pathogenesis will be clarified.

SUMMARY

Amino acid chromatograms of serum and urine were obtained from patients with epilepsy and encephalitis before, during, and after convulsions and were compared with those of normal children.

Increased aminoaciduria with normal levels of amino acids in the serum was

observed in 13 of 16 patients during periods of active convulsions and appears to be related to the severity of the seizures.

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STRONGYLOIDIASIS

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WHILE strongyloidiasis infection is found in all ages, the incidence of this condition in the childhood age group is not wholly appreciated, nor is the potential seriousness of the disease usually recognized. Because of the paucity of material on this subject in the pediatric literature, this series of 16 cases of strongyloidiasis, including 3 autopsied cases, is presented in the hope that those concerned with the care of children will be reminded of the potentially serious nature of this infection.

INCIDENCE AND GEOGRAPHICAL DISTRIBUTION

The distribution of the disease is worldwide, the greatest incidence being found in moist tropics.[1] A conservative estimate of the incidence in North America is 400,000 infected people, compared to 35 million in the world. One to five per cent of people in the southern United States are infected, compared to less than 1 per cent in the northern United States[2]; only scattered cases are reported in Canada.[3] Mexico and South America have at least 10 million cases. There seems to be a seasonal variation, with the greatest incidence in late summer and early autumn. Negroes are affected about four times less frequently than other races.[4] Several series indicate that at least 50 per cent of the occurrences of strongyloidiasis were in persons less than 20 years of age.[4]

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LIFE CYCLE

In order to understand fully the pathology and symptomatology produced by *Strongyloides stercoralis*, it is necessary to know the life cycle of this parasite, which is similar to that of the hookworm.[5] The filariform larvae develop in soil and infest the host by penetrating the skin, passing through the lymph and blood channels to the lungs, and then to the small intestine via the bronchial mucosa and esophageal route; there they develop into adults who mate. The females burrow into the intestinal mucosa where they lay eggs which hatch into rhabditiform larvae. The latter return to the lumen of the intestine where they may follow one of two courses: (1) they may develop into filariform larvae which are infective for man; (2) autoinfection may occur by means of dwarf filariform larvae (a) penetrating the perianal skin or (b) invading the ileum and colon from which the filariform larvae pass back to the lungs and renew the cycle.[5, 6]

Using dogs as the experimental hosts, Faust[7] established that the lung phase occurred 3 to 30 days after the skin was infected and that the intestinal phase occurred as early as 11 days after the skin infection. He also demonstrated that most forms of the parasite could be found in the bronchioles, thus theoretically allowing a third means of autoinfection.[7]

Although the parasite cannot endure refrigeration and lives less than 7 days in moist soil, it maintains itself in the soil by the free-living cycle.[8]

CLINICAL ANALYSIS OF VANDERBILT HOSPITAL CASES

Sixteen cases of stronglyloidiasis have been diagnosed at Vanderbilt University Hospital since 1936, 8 of which were in males and 8 in females. Fifteen were in white patients and one in a Negro; 9 were in children and 7 were in adults. The children's ages ranged from 16 months to 8 years.

Three patients complained of abdominal pain, 4 of weakness and imperfect locomotion, 3 of diarrhea, and 3 of swelling of the extremities; other complaints were vomiting, "worms," meningitis, bumps on the legs, and "fits."

Parasitic infection was one of the initial clinical impressions in 5 of the 9 infected children, the nephrotic syndrome in 3, and malnutrition in 4; acrodynia, celiac syndrome, multivitamin deficiencies, pneumonia, and penicillin reaction were each listed one time in a differential diagnosis. Strongyloides was found on routine stool examination in 2 children, one of whom had meningococcal meningitis and the other one, hypoparathyroidism.

In adults parasitic infection was listed as one of the clinical impressions in 2 of the 7 cases, gastrointestinal malignancy in 2, and nephrosis in 2; leukemia, anxiety state, gallbladder disease, ulcerative colitis, riboflavin deficiency, and atypical pneumonia were each listed once.

The signs and symptoms found in all 16 patients were in general the usual ones recorded in the literature. Diarrhea, vomiting, and weight loss were the most frequent symptoms, each being present in 9 cases. Weakness was present in 8 cases, abdominal pain in 7, and anorexia, fever, or a semistuporous state in 5. Edema was the most common sign, being found in 9 cases, a somewhat greater incidence than has been previously reported. Melena was reported in 4 cases; urticaria, cough, and dyspnea appeared in 6. Other signs and symptoms which appeared less frequently were constipation, nausea, indigestion, malaise, and headache.

Eosinophilia, present in 13 cases, was the most constant laboratory finding. Anemia was present in 11 patients, leukocytosis in 10, and occult melena in 5. Hypoproteinemia, another finding not heretofore reported, was present in 5 patients.

In 15 patients the larval forms were found in stool specimens, the remaining case was diagnosed at postmortem examination.

Of the 16 cases, 11 were treated with gentian violet only, 3 with Hetrazan, 1 with Delvex, and 1 received no treatment. Only 1 patient is known to be cured; 1 is presumed to be cured; 4 are presumed to be still infected; 2 are known to be still infected; and 5 are completely lost to follow-up. Three patients were examined at post mortem.

CASE REPORTS

CASE 1 (1958).—A 16-month-old white girl was admitted to Vanderbilt Hospital with an illness of 5 weeks' duration, which started with progressive anorexia, vomiting, irritability, and lethargy. Approximately 2 weeks prior to admission to this hospital she was admitted to another hospital with the tentative diagnosis of pneumonia.

After 12 days of therapy with antibiotics and intravenous fluids she was discharged as unimproved. Shortly thereafter she developed diarrhea and was brought to Vanderbilt Hospital.

Physical examination revealed normal vital signs, pallor, pedal edema, malnutrition, and a distended abdomen. Hemoglobin was 6.3 Gm. per cent. The white blood cell count varied from 1,000 to 15,000 per cubic millimeter, with 12 per cent eosinophils. Total serum protein was 2.1 Gm. per 100 ml. (1.1 Gm. per 100 ml., albumin). The serum sodium and chloride levels were low. Stools were guaiac-positive and *Strongyloides stercoralis* larvae were seen on one occasion.

In spite of vigorous therapy with parenteral fluids, blood, albumin, Chloromycetin, and Hetrazan, she had persistent vomiting and abdominal distention and died on the ninth hospital day, apparently from severe respiratory distress.

Postmortem examination (V-58-179) revealed a malnourished infant with marked abdominal distention. There was moderate effusion in all serous cavities.

The lungs showed extensive pulmonary hemorrhage, rare strongyloides larvae, and little inflammatory response. In the submucosa of the trachea numerous foreign-body type granulomatous reactions were present, in which no parasites were seen.

The duodenum and proximal jejunum were marked by innumerable small ulcerations. Larval and adult *Strongyloides stercorales* were recovered in large numbers in the intestinal contents. On microscopic examination it was found the duodenal and jejunal ulcerations extended deep into the submucosa where there was intense acute and chronic inflammatory change. Adult worms, larvae, and ova were present in large numbers in the mucosa and submucosa.

The entire colon showed extensive submucosal hemorrhage and early mucosal ulceration. Numerous filariform larvae were present in the submucosal veins, lymphatics, lymphoid follicles, and tissue spaces. The inflammatory responses were minimal. There was severe fatty change in the liver. No other significant abnormalities were present.

CASE 2 (1956).—A 3½-year-old white boy was transferred to Vanderbilt Hospital from a local hospital because of uncontrolled vomiting and diarrhea. Three and one-half weeks prior to admission the child had a generalized rash of several days' duration which was felt by the family to be measles. He recovered promptly but several days later he developed vomiting, diarrhea, fever, pedal and serotal edema, and abdominal distention. He was admitted to another hospital where the vomiting and diarrhea persisted while he was on extensive antibiotic therapy. He was reported to have passed two "long, large worms" while in the hospital.

Physical examination on admission revealed pedal edema, pallor, perianal erythema, and normal vital signs. Laboratory studies revealed a total serum protein of 2.6 Gm. per 100 ml. (1.6 Gm. per 100 ml., albumin), low serum sodium, potassium, and chloride, and a white blood cell count of 5,000 per cubic millimeter, with 28 per cent eosinophils. Large numbers of *Strongyloides stercoralis* were present in the stool. The admission hemoglobin of 10.8 Gm. per cent fell to 8.0 Gm. per cent after partial dehydration.

In spite of intensive parenteral fluid therapy and antibiotics no significant correction of the electrolyte imbalance was established. His course was marked by ileus, persistent vomiting, tetany, seizures, electrocardiographic abnormalities, and fever. Terminally, he developed congestive failure and died on the twelfth hospital day.

Postmortem examination (V-56-90) revealed infection with *Strongyloides stercoralis* in the small and large intestines. An ulcerative colitis was present grossly, and on microscopic examination innumerable strongyloides larvae and monilial forms were

found to be present. There was a hemorrhagic pneumonia in which aspergilli were apparently growing; no strongyloides forms were seen. Blood culture was positive for *Escherichia coli*. Additional findings were hemorrhage and degeneration of the adrenals, severe fatty infiltration of the liver, and anasarca.

CASE 3 (1936).—A 1½-year-old white girl was admitted to Vanderbilt Hospital with a 3-week history of diarrhea, weight loss, abdominal distention, and occasional vomiting.

Physical examination revealed a wasted infant with a temperature of 100° F., edema of the legs, and a distended abdomen. Significant laboratory findings were 1+ albuminuria and the presence of ascaris in the stool.

She was treated with parenteral fluids, but diarrhea and progressive debilitation continued and she died on the ninth hospital day.

Postmortem examination (V-36-119) revealed large numbers of ascaris and strongyloides larvae in the intestinal contents. There was infiltration of the submucosa of the small and large intestines with leukocytes, predominantly eosinophils. Several strongyloides ova were seen in the ileum, but no parasites or ulcerations were noted in the ileum or colon. The lungs showed congestion, edema, numerous small hemorrhages, and an occasional strongyloides larva in the area of the hemorrhage.

PATHOGENESIS

The portal of entry of this parasite is thought to be a cutaneous surface in most instances; the site of invasion may be marked by erythema, edema, and pruritus. However, a rash was noted (historically only) in one of our patients and was thought to have been a mild case of measles. Failure to document a lesion at the portal of entry may be because: (1) the invasion did not produce a significant rash, or (2) the initial infection was remote and the terminal illness was due to autoinfection as in fatal cases of strongyloidiasis occurring years after the patient has left an endemic area.[8]

Following cutaneous entry, the infective filariform larvae pass to the pulmonary capillaries where they egress, enter the alveolar spaces, and produce hemorrhages by disruption of the capillary walls. All 3 of our autopsied patients showed pulmonary hemorrhage. In Case 1 hemorrhage was severe and there was little inflammatory reaction and no evidence of secondary infection. In Case 2 the severe hemorrhage was complicated by a mycotic pneumonitis thought to be secondary to debilitation and pulmonary injury. In the third case small hemorrhages were the predominant lesions. Rare *Strongyloides stercoralis* larvae were demonstrated in the lungs in Cases 1 and 3.

Following the entry of the filariform larvae into the alveolar spaces, the organisms ascend the tracheobronchial tree and enter the gastrointestinal tract. During this part of the migration, maturation into adult forms is occurring. It has been reported that some of the maturing larvae may invade the mucosal glands of the trachea or bronchi, possibly causing the granulomatous reaction in the submucosal glands of the trachea noted in Case 1. These lesions consisted of necrotic debris, multinucleated giant cells and chronic inflammatory cells; no parasites could be found. Sections of the trachea and large bronchi were not taken in Cases 2 and 3.

The mature impregnated females invade the intestinal mucosa distal to the pylorus, predominantly in the duodenum and jejunum, but invasion

may occur at any level. Adult worms and ova were seen in the submucosa of the small intestine of our three autopsied patients and there were definite ulcerations in two. In the third case, although numerous *Strongyloides stercorales* were found in the fecal material, no ulcerations or invading organisms were demonstrated on histologic examination.

In 2 cases there was a severe colitis, with innumerable filariform larvae in the colonic submucosa. In the third case only congestion and eosinophilic infiltrate were demonstrable. Apparently in 2 patients the colon was the site of extensive autoinfection and in both of these children severe pulmonary hemorrhage was observed at postmortem examination. Since with colonic autoinfection the filariform larvae pass through the lungs again, it seems reasonable that at this time the pulmonary infection might be heavy enough to cause respiratory failure.

Other findings in all 3 cases were those expected with debilitation, malnutrition, and secondary infection, i.e., edema, emaciation, fatty liver, and moniliasis. It is not clear whether the malnutrition renders the individual more susceptible to strongyloides or whether the overwhelming infection produces debility. Perhaps both suppositions are true.

Rare lesions (not seen in our cases) described in the literature include involvement of the gallbladder, liver, stomach, lymph nodes, pericardium, and genitourinary tract.[8, 11, 12, 13]

DIAGNOSIS

The diagnosis of the disorder is based on fitting together symptoms, signs, laboratory findings, radiographic findings, and skin and precipitin tests, and demonstration of the characteristic larvae in either stools or duodenal aspirate by microscopy or by a special stool-culture method. Although none of the symptoms or signs is diagnostic by itself, certain of these occur with such frequency that their appearance should make one suspicious of strongyloidiasis. One of the most frequently found symptoms is abdominal pain, which may be diffuse, well localized, colicky, gnawing, dull or heavy, and variably effected by eating. Diarrhea is a common finding and it may occasionally be bloody. Nausea, vomiting, anorexia, and indigestion all occur frequently. Malaise, weakness, and headache complete this nonspecific group of symptoms.

Occasionally, cough and, less frequently, hemoptysis and/or dyspnea occur; rarely, pulmonary symptoms are severe enough to suggest pulmonary tuberculosis.[16]

Certain of the commonly occurring signs include fever, urticaria, edema, and jaundice. Abdominal tenderness is such a frequent finding that in one series of 100 cases, 32 patients underwent laparotomy.[17]

Frequently occurring laboratory findings include anemia, leukocytosis, hypoproteinemia, occult melena, and eosinophilia. The last is found in almost 100 per cent of cases. Suggestive roentgenographic evidence is the finding of a pipe-stem picture in the second and third parts of the duodenum. Transit time in the affected loops of duodenum is said to be slowed.[18]

The skin test, though nonspecific, has a place in the diagnostic work-up.

With the use of a contaminant-free filariform larval extract, an antigen is prepared which is injected intradermally. The reaction produced is of the immediate type and is read 15 minutes after injection. An adjunct to this is the precipitin test, in which the same larval antigen is used and the patient's serum is used for the antibody vehicle. Both of these tests were positive in 23 of 25 patients in whom the disease had been proved by stool microscopy.[19]

The sine qua non for diagnosis is the demonstration of the characteristic rhabditiform larvae in stool specimens or in duodenal aspirate. A patient should not be considered cured until both duodenal aspirate and stool are free of the parasites.

There is still another means of diagnosing this condition, viz., by a special stool culture. About one ounce of fresh feces is mixed with an equal amount of moist garden soil, previously sterilized. This mixture is then kept in a warm, dark spot for 7 days. At the end of the incubation period the container is covered with multiple layers of gauze, a 6-inch filter funnel is filled with water, and the gauze-covered container is placed in the funnel so that the water level just touches the gauze. The larvae, if present, can be seen to migrate to the warm fluid in the funnel. Subsequent examination microscopically of the filtrate will reveal the larvae.[9]

PROPHYLAXIS AND TREATMENT

Prophylaxis of the disease is based on the proper disposal of feces, the wearing of shoes, and otherwise avoiding contact with soil known to be contaminated.

The problem of eradication has been a difficult one since the parasite was first identified in 1876 by Normand. Glycerin, sulfur, castor oil, kerosene, thymol, oil of chenopodium, carbon tetrachloride, and alcohol have all been used.[20] Faust in 1931 first suggested the use of gentian violet[21] and, though it has been proved relatively ineffective, it is still the most commonly used drug.[22] Its ineffectiveness when given intravenously is also known; in one report of 15 cases, there were no cures, and in each of these there was the complicating factor of venous thrombosis.[23]

Among the more recently tried group of drugs, including miracil D, Mantomide, Phenergan, stibophen, hexylresorcinol, quinacrine, tetracycline, fumagillin, Purpomycin, piperazine, and Hetrazan, the last has probably had the most success. However, its effectiveness has also been limited. This drug produced negative stools in only 2 of 7 cases treated; toxic manifestations included nausea, vomiting, diarrhea, weakness, and epigastric pain.[24]

The newest and most promising anthelminthic is dithiazanine (Delvex and Abminthic).[25, 26] It must be given orally since it is damaging to renal tubules if given parenterally. It is helminthicidal only to the adult female form. In a study of 18 patients who were treated with 200 mg. three times per day for 5 to 21 days, 16 patients were found to be free of the parasite, having no larval forms in either duodenal aspirate or stools. Side reactions are said to be minimal; these include nausea, which at times is severe, and vomiting and diarrhea, which are usually transient.

There is also the possibility of a spontaneous cure according to one author reporting on a series of patients in a Japanese prison camp where many of those known to be infected with the organism recovered without treatment.[27]

SUMMARY

A report of 16 cases of strongyloidiasis, including 3 fatal cases with autopsies in children, and a review of the literature are presented. An effort has been made to emphasize the more important clinical and pathologic features of this disease.

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EPIDEMIOLOGIC, CLINICAL, AND LABORATORY FEATURES OF AN EPIDEMIC OF TYPE 9 ECHO VIRUS MENINGITIS

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SINCE Wallgren[1] first introduced the term "aseptic meningitis" in 1925, tissue culture techniques have become available which have made possible the isolation of a number of viruses from the cerebrospinal fluid of patients with this syndrome. These observations have established a more varied etiology than Wallgren originally considered and suggest the term "meningitis of virus origin" as first used by Rotem[2] as more accurately descriptive of this group of diseases.

Members of the ECHO group of viruses were first associated with aseptic meningitis in 1954 when a type 6 strain was isolated from patients with this syndrome.[3, 4]

Type 9 ECHO virus or similar agents were first implicated in minor epidemics of nonbacterial infection of the meninges in Great Britain in 1954 and 1955.[5, 6] In the summer of 1956, however, widespread outbreaks of the same type of disease, many of them with a high incidence of rash, were reported from Great Britain,[2, 7, 8] the low countries,[9] Switzerland,[10] West Germany,[11, 12] Scandinavia,[13, 14] and Canada.[15, 16] Epidemics caused by this agent were again noted in 1957 in Canada,[17-19] Milwaukee,[20] and Minnesota.[21]

ECHO virus type 9 was first isolated from the spinal fluid of patients with aseptic meningitis in Massachusetts in 1957[22]; in 1958, Frothingham[23] reported 3 cases from Boston in which a rash similar to that present in meningococcemia was noted and in which the same virus was thought to be the causative agent.

The purpose of this paper is to describe the clinical features and virologic findings in a group of 64 cases of "aseptic" meningitis which occurred in the Boston area in the summer of 1958, the majority of which were proved to be due to infection with type 9 ECHO virus.

LABORATORY METHODS

Stools and spinal fluids were obtained soon after the patients were admitted to the hospital. Within 12 to 24 hours after collection, the stools were suspended in Hank's balanced salt solution containing 500 units of penicillin, 500 units of streptomycin, and 100 units of nystatin per milliliter. Prepared stool suspensions and spinal fluids were stored at –20° C. until inoculation into tissue culture. Acute and convalescent serums were drawn at an interval of at least one

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week. Most of the late specimens were obtained long after discharge of the patient from the hospital, as long as 4 to 5 months in some instances.

Primary cell cultures of human amnion and Rhesus monkey kidney were used for isolation and identification of virus; only the latter were employed in neutralization tests. The cells were washed and resuspended in Melnick's lacto-albumin hydrolysate medium.[24] One milliliter of the suspension containing 500,000 cells was distributed into a number of test tubes. The cultures were incubated at 36° C. in a stationary position. Maintenance medium consisted of 5 per cent horse serum, 5 per cent calf embryonic extract, 45 per cent calf amniotic fluid, and 45 per cent Hank's balanced salt solution. Human amnion cells were grown in 20 per cent horse serum, 0.045 per cent glutamine, and 80 per cent Hank's balanced salt solution. The maintenance medium used was the same as with the monkey kidney cell cultures.

After removal from the refrigerator, the stool specimens were centrifuged at a slow speed to remove the large particles and the supernate spun at 4,500 r.p.m. in a refrigerated centrifuge for 45 minutes. One milliliter of the clear supernate was inoculated into one tube each of monkey kidney and amnion cultures from which the fluid had been removed. After incubation at 36° C. for one hour, the fluid was poured off and fresh medium added. The cultures were examined daily. Those which showed cell degeneration were transferred once to monkey kidney cultures. The same type of culture was used to carry out the tests necessary to identify the isolated virus. These tests were performed in the following manner: Each of the viral strains isolated from the patients was diluted to 10^{-3} and 10^{-5} and mixed with a 1:25 dilution of known type 9 ECHO antiserum. After one hour's incubation at room temperature, 0.1 ml. of the mixture was inoculated into tissue cultures; these were examined every day for 5 days. If partial neutralization was observed, the test was repeated using the technique recommended by the committee on ECHO viruses.[25]

Titration of neutralizing antibodies in the serum of patients was also carried out in monkey kidney tissue cultures. The specimens to be examined were inactivated by heating to 56° C. for 30 minutes. They were then serially diluted (1:4 and up) and mixed with an equal volume of fluid containing 100 TCP_{50} of type 9 ECHO virus; a strain freshly isolated from spinal fluid was used. Following incubation for one hour at room temperature, 0.1 ml. of the serum-virus mixture was inoculated into each of a series of tissue culture tubes. Virus controls consisted of 100, 10, and 1 TCP_{50} doses. All cultures were studied microscopically daily for one week. The highest dilution of serum completely preventing cell degeneration was considered to be the neutralizing titer.

RESULTS

Epidemiology.—From July 12 to the end of September, 1958, 64 patients with nonbacterial or "aseptic" meningitis were admitted to the New England Medical Center; 55 children were hospitalized at the Boston Floating Hospital and 9 adults at the New England Center Hospital.

The great majority of cases came either from the city of Boston itself or from towns south of it. The relative absence of patients from communities to the north (only 7) was probably due to the fact that referrals to the Boston Floating Hospital of all types of disease from this area are generally infrequent.

The age of the patients ranged from 3 months to 30 years (Fig. 1). Three were under 6 months and 5 under 1 year of age; over 5 per cent were 4 to 9 years old. The great majority were less than 10 years of age. The highest incidence was in individuals aged 7 to 8 years. A similar age distribution has been noted by other observers.[7, 8, 15, 17, 20]

Forty-five of the patients were male and 19 female. These findings confirm the previously described predominance of males with this disease.[2, 8, 17, 20]

Fig. 2 shows the seasonal distribution of illness in the group. Thirty-two (50 per cent) had onset of symptoms in the last week of July or the first 2 weeks of August.

Of the 56 patients less than 20 years of age, 14 (25 per cent) had a history of family contact, one or more of their siblings having had symptoms of respiratory or gastrointestinal disease or both; some of these had had a skin eruption within 2 weeks of onset of the patient's illness. In the 56 children studied, there were 2 sets of 2 siblings. In 4 of the 56 patients under age 20 (7 per cent) there was a contact history among friends or neighbors.

Of the 8 adults, 5 (62.5 per cent) had children with respiratory and/or gastrointestinal symptoms with fever, usually within a week prior to the parent's admission to the hospital. Two of these contacts had a rash. One adult had been on a submarine cruise prior to admission; an undefined respiratory disease was prevalent among the crew. The data summarized in Table I indicate a history of probable contact in 37.5 per cent of the entire group of 64 patients.

Clinical Features.—The first manifestations of disease appeared in from 3 weeks to less than one day prior to admission to the hospital. In 11 patients (17 per cent) there was a biphasic picture; the initial illness lasted for several days, was followed by an asymptomatic period of varying duration, and then symptoms recurred.

As noted in Table II, headache, fever, nausea, and vomiting were the most common symptoms; all of the patients able to give a history complained of headache.

Although all but one of the patients had had fever sometime in the course of the disease, 6 (5 children, 1 adult) had been afebrile until entry to the hospital. Maximum rectal temperatures recorded during the period of hospitalization varied from 99.8° F. to 105.6° F., exceeding 103° F. in 16 patients (25 per cent) and ranging between 101 and 103° F. in 33 (52 per cent). After admission the duration

TABLE I. CONTACT HISTORY IN 64 CASES OF VIRAL MENINGITIS

AGE (YEARS)	TOTAL NO. OF CASES	FAMILY CONTACT		OTHER CONTACTS		ALL CONTACTS	
		NO.	%	NO.	%	NO.	%
20	56	14	25	4	7	18	32
20	8	5	62.5	1	12.5	6	75
All	64	19	30	5	17.5	24	37.5

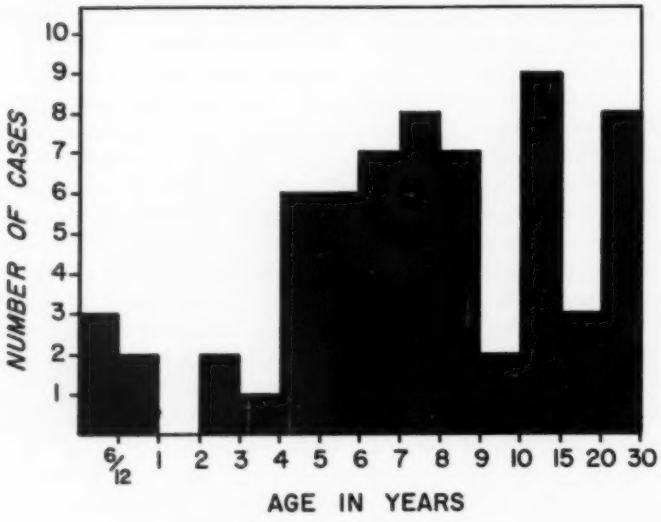

Fig. 1.—Age distribution.

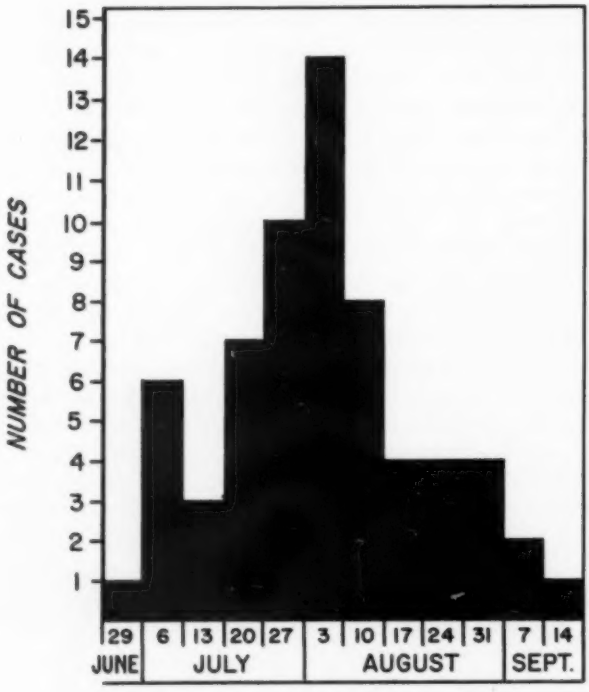

Fig. 2.—Week of onset of symptoms (1958).

TABLE II. SYMPTOMS AND SIGNS IN 64 PATIENTS WITH VIRAL MENINGITIS

SIGNS OR SYMPTOMS	AGE (YEARS) 0-4 (14 PATIENTS) NO.	%	5-9 (30 PATIENTS) NO.	%	10-19 (12 PATIENTS) NO.	%	OVER 20 (8 PATIENTS) NO.	%	ALL CASES (64 PATIENTS) NO.	%
Headache	8*	57	30	100	12	100	8	100	58*	91
Fever	14	100	30	100	11	92	8	100	63	98
Nausea and vomiting	10	71	25	83	11	92	3	37.5	49	77
Rash	9	64	8	27	1	8	0	0	18	28
Abdominal pain	4	29	9	30	4	33	0	0	17	27
Abdominal tenderness or guarding	2	14	2	7	2	17	0	0	6	9
Nuchal rigidity										
Slight	2	14	14	47	3	25	1	12.5	20	31
Moderate	4	29	7	23	3	25	4	50	18	28
Marked	0	0	3	10	4	33	0	0	7	11
Absent	8	57	6	20	2	17	3	37.5	19	30
Kernig's sign	0	0	3	10	2	17	1	12.5	6	9
Brudzinski's sign	2	14	1	3.3	0	0	0	0	3	5
Coryza (by history)	2	14	3	10	1	8	1	12.5	7	11
Cough (by history)	3	21	7	23	0	0	0	0	10	16
Sore throat (by history)	0	0	4	13	2	17	0	0	6	9
Pharyngitis										
Exudative	3	21	1	3	1	8	1	12.5	6	9
Nonexudative	4	29	10	33	4	33	1	12.5	19	30
Pain on eye motion	0	0	0	0	1	8	6	75	7	11
Photophobia	0	0	0	0	1	8	4	50	5	8
Diarrhea	2	14	3	10	1	8	0	0	6	9
Chills	1	7	3	10	0	0	1	12.5	5	8
Hepatomegaly	0	0	3	10	2	17	0	0	5	8
Generalized muscle aches	0	0	4	13	1	8	1	12.5	6	9
Cervical lymphadenopathy	1	7	1	3	0	0	0	0	2	3
Backache	0	0	1	3	0	0	3	37.5	4	6

*The 6 patients in whom headache was not noted were unable to give a history; 5 were under 1 year of age; the sixth was age 2 and mentally retarded.

of the temperature elevation ranged from 12 hours to 7 days; a secondary rise was observed in 12 instances (19 per cent).

Nausea or vomiting or both were noted in 46 (80 per cent) of the 56 individuals under age 20 and in only 3 (37.5 per cent) of the 8 adults. Abdominal pain was present only in children; seventeen of 56 patients (30 per cent) less than 20 years old had this symptom.

A skin eruption was noted in 18 patients (28 per cent), only one of whom was older than 10 years. The incidence of rash in the group less than 10 years of age was 39 per cent. It was present in 9 of 14 patients younger than 5 years (64 per cent). The exanthem occurred at varying times in the course of the illness. In 16 instances it was fully developed at the time of admission to the hospital. It usually involved the face but was also observed on the thorax, neck, and abdomen and was predominantly macular or maculopapular in character. In 3 patients petechiae were also observed. In 3 other cases the eruption was entirely petechial. The maximal duration of the skin lesions was 2 days. No enanthem was noted.

Symptoms of upper respiratory infection were not prominent. Cough, coryza, and sore throat were present in 16, 7, and 9 per cent, respectively, of the patients. It is noteworthy that only one adult complained of coryza.

In contrast to the low incidence of complaint of pharyngeal discomfort, a total of 25 patients (39 per cent) had pharyngitis when examined; exudate was present in 6 cases. Of the 25 individuals with demonstrable involvement of the pharynx, 18 (72 per cent) were under 10 years of age. Earache was present in one instance and otitis media was found by physical examination in 2 others.

Nuchal rigidity was demonstrable in 70 per cent of the group. Of considerable interest is the fact that it was only slight or entirely absent in 61 per cent. Marked stiffness of the neck was present in only 11 per cent of the cases. The possible importance of this finding in differentiating nonbacterial from bacterial meningitis will be commented upon later. Kernig's sign was elicited in only 6 patients (9 per cent) and Brudzinski's sign in 3 (5 per cent).

Other clinical findings included pain on motion of the eyes, photophobia, diarrhea, generalized muscle aching, chills, backache, hyperacusis, blurring of vision, tinnitus, hepatomegaly, and cervical lymphadenopathy. The frequency and age distribution of these manifestations are presented in Table II. A 14-year-old boy complained of severe anterior chest pain and dyspnea, suggesting epidemic pleurodynia. Electrocardiogram and x-ray study of the chest were normal; ECHO virus (type 9) was isolated from his spinal fluid and he exhibited a greater than fourfold rise in neutralizing antibody titer to this agent.

Muscular weakness was not demonstrated in any of the cases by complete muscle examination carried out shortly before discharge from the hospital.

Four patients had evidence suggestive of more extensive involvement of the central nervous system than simple meningitis. One had hallucinations, 2 were noted to "talk out of context," and one (1 year old) had a generalized seizure which occured with a sudden rise in fever and may have been a "febrile convulsion." The last 3 had proved ECHO virus (type 9) infection.

Despite the often fulminating onset of illness, the course of the disease was invariably benign. No permanent residua attributable to the viral meningitis were noted even after several months.

Laboratory Findings.—The total number of white cells in the spinal fluid obtained on admission ranged from 0 to 1,620 per cubic millimeter (Table III). Contrary to other reports,[2, 8, 9, 10, 19, 20] the counts did not exceed 200 per cubic millimeter in any of the individuals in this group. It is interesting to note that 2 of 4 patients with less than 10 cells per cubic millimeter were adults. Each had only one lymphocyte per cubic millimeter; type 9 ECHO virus was isolated from the cerebrospinal fluid of one.

TABLE III. NUMBER OF CELLS IN CEREBROSPINAL FLUID

	NO. OF CELLS PER CUBIC MILLIMETER				
	10	10-99	100-499	500-999	1,000-1,620
No. of cases	4	17	22	16	5
Per cent of total group	6	27	34	25	8

Lymphocytes predominated in the spinal fluid in 50 cases (78 per cent) while neutrophils were more numerous in 12 instances (19 per cent). One

patient showed equal numbers of both types of cells and one had no cells. The differential counts varied from 100 per cent lymphocytes to 90 per cent neutrophils. It should be pointed out, however, that in 5 patients with more than 1,000 cells per cubic millimeter there was a predominance of lymphocytes in every instance.

Data concerning the quantity of protein in the spinal fluid of the entire group of patients are presented in Table IV. Striking is the fact that a majority (61 per cent) had normal levels. Of the 3 individuals with more than 100 mg. per 100 ml. one was an adult (102 mg. per cent), another a 4-month-old child (200 mg. per cent) whose spinal fluid was bloody because of a traumatic tap, and the third a 14-year-old boy (140 mg. per cent) with 355 cells per cubic millimeter (85 per cent lymphocytes). In contrast to the great majority of children in whom spinal fluid protein was normal, it was elevated in 7 of 8 adults. The ratio of spinal fluid sugar to simultaneously drawn blood sugar was less than 50 per cent in only 8 patients (12.5 per cent); in 7 it was 40 per cent or more. In one case it was less than 34 per cent; an infusion of glucose and water had been started 10 minutes before the blood sugar was drawn. No organisms were seen on gram stain of spinal fluid sediment in any patient, and all cultures were sterile.

TABLE IV. LEVELS OF SPINAL FLUID PROTEIN

	PROTEIN (MG. PER 100 ML.)		
	< 45	45-100	100-200
No. of cases	39	22	3
Per cent of total group	61	34	5

Most of the patients (56 per cent) had normal peripheral white blood cell counts (Table V). None had leukopenia; this finding is at variance with other descriptions of this syndrome.[2, 19, 20] Contrary to the usual impression that the white blood count is normal or low in viral infections, it was higher than 10,000 per cubic millimeter in 44 per cent of the cases. It has been stated that a predominance of lymphocytes is characteristic of viral infections. In 61 of the patients studied (95 per cent) neutrophils were most numerous; 80 per cent or more were demonstrated in 30 per cent of the group. Lymphocytes predominated in the peripheral blood in only 2 individuals.

TABLE V. PERIPHERAL WHITE BLOOD COUNTS

	WHITE BLOOD CELLS PER CUBIC MILLIMETER				
	< 5,000	5-10,000	10-15,000	15-20,000	20,000
No. of cases	0	36	24	2	2
Per cent of total group	0	56	38	3	3

The sedimentation rate was elevated in 37 of the 43 patients (86 per cent) in whom this determination was carried out. In only 5 cases (12 per cent) was the rate higher than 50 mm. per hour by the Westergren method; the highest value was 86 mm. per hour.

Varying degrees of proteinuria were observed in 10 patients at the time of admission to the hospital; this disappeared rapidly. Eleven patients had slight pyuria and 3 had microscopic hematuria when they arrived on the wards. These abnormalities were detected only during the early period of fever.

Virologic and Serologic Studies.—ECHO virus, type 9, was proved to be the etiological agent in 45 of the cases (70 per cent) by isolation of the virus from the spinal fluid or by demonstration of a fourfold or greater increase in neutralizing antibody titer or by both. In 5 other patients (8 per cent), ECHO virus was thought to be the causative organism despite failure to isolate it from the spinal fluid and absence of a significant rise in antibody. These cases are described in detail below.

A 5-year-old boy with a history of a biphasic illness, a maculopapular rash, moderate nuchal rigidity, and no cells in the spinal fluid yielded ECHO virus, type 9, in 2 separate stool specimens but not from the cerebrospinal fluid; paired sera were not obtained for study.

A 10-year-old girl whose brother had proved active type 9 ECHO meningitis at the time she was admitted to the hospital revealed the same agent in one stool specimen. The antibody titer of acute and convalescent serums was 1:128; the first serum was not obtained until 2 weeks after the onset of the illness and the last 3 months later. Spinal fluid was not cultured for virus.

In 3 other patients from whom virus was not isolated, the initial antibody titer was high (1:32 in one and 1:64 in the others), and the rise was only twofold. Acute serum was drawn only 9 to 10 days after onset of symptoms in all of these individuals, however.

In 14 cases (22 per cent), no etiological agent could be demonstrated. It should be pointed out that specimens adequate for virologic or serologic study were not obtained in 12 of these. In 2 other patients, virus was not isolated and initial acute phase antibody titers of 1:4 and 1:8, respectively, did not rise during convalescence. These results are summarized in Table VI.

The data in Table VI indicate that the recovery rate of virus from the spinal fluid (50 per cent) was approximately twice that from stool (26 per cent). The ease with which this virus can be isolated from spinal fluid has been noted by several observers.[9, 17-20]

Of the 9 patients whose paired sera failed to show a fourfold increase in neutralizing antibody titer to type 9 ECHO virus, 2 have been included in the "etiology not proved" group, and 4 were considered as probably having ECHO virus infection. The other individuals who failed to show antibody rise are worthy of further comment.

An 8-year-old boy with 1,620 cells per cubic millimeter (the highest in the group) and type 9 ECHO virus in the spinal fluid had a neutralizing titer of 1:64 four days after onset of symptoms and 1:32 two weeks later.

A 7-year-old youngster with 1,391 white cells per cubic millimeter and type 9 ECHO virus in the spinal fluid had an antibody titer of 1:32 seven days after onset of symptoms and 1:64 four months later.

TABLE VI. SUMMARY OF RESULTS OF VIROLOGIC AND SEROLOGIC STUDIES

	NO. OF CASES TESTED	POSITIVE FOR TYPE 9 ECHO VIRUS		NEGATIVE FOR TYPE 9 ECHO VIRUS	
		NO.	%	NO.	%
Cerebrospinal fluid	50	25	50	25	50
Stool	35	9	26	26*	74
Neutralizing antibody	47	38†	81	9†	19

*An unidentified virus isolated from one stool specimen.

†Positive indicates fourfold or greater increase in titer. Negative denotes a fourfold rise, no increase, or a decrease in level of neutralizing antibody.

A 3-month-old baby with 46 white blood cells per cubic millimeter and type 9 ECHO virus in the spinal fluid had acute and convalescent antibody titers of 1:256; the first specimen was obtained one day after onset of illness and the second 4 weeks later.

There were 7 cases of proved or probable type 9 ECHO virus meningitis in which a fourfold rise in antibody titer could not be demonstrated but in which neutralizing levels of 1:32 to 1:256 were present. In 5 of these the initial serum specimen was obtained 7 to 14 days after the beginning of illness; this is sufficient time for a significant increase in titer to develop. The antibody titer in the sixth case was 1:256 one day after onset of symptoms, but, since the patient was only 3 months old, it is possible that the disease had been present for some time before it was suspected. In only one case of proved type 9 ECHO virus meningitis is it difficult to explain the lack of rise in titer of neutralizing capacity of the serum.

DISCUSSION AND SUMMARY

Many investigators have commented on the relatively benign, self-limited nature of type 9 ECHO virus meningitis; this study confirms this observation.

The differentiation of viral from bacterial meningitis is of crucial importance, especially when a rash, particularly a petechial one, is present. Description of a case of bacterial infection of the meninges observed during the ECHO virus outbreak is of pertinence in this regard. A 7-year-old boy was admitted at the height of the epidemic of "aseptic" meningitis with a history of fever, nausea, and vomiting of 3 days' duration and headache for one day. Physical examination showed a temperature of 100.6° F. rectally, no rash, marked nuchal rigidity with positive Kernig's sign. There were 2,500 white blood cells per cubic millimeter (91 per cent neutrophils and 9 per cent lymphocytes) in the spinal fluid; the ratio of sugar to simultaneously drawn blood sugar was 37 per cent, and the protein content 40 mg. per 100 ml. Peripheral white blood count was 7,250 with 80 per cent neutrophils. No organisms were seen on gram stain of the spinal fluid sediment. The child did not appear very ill and was thought to have nonbacterial meningitis; however, because of the large number of cells in the spinal fluid and the predominance of neutrophils, the possibility of bacterial infection was seriously considered. Lumbar puncture on the day after admission revealed 3,500 white blood cells per cubic millimeter with 85 per cent neutrophils. The cerebrospinal fluid to blood sugar ratio was 19 per cent and the protein had increased to 135 mg. per 100 ml. Despite the persistent absence of organisms on smear, antimicrobial therapy was started because of the marked decrease in cerebrospinal fluid sugar. *Neisseria meningitidis* was subsequently cultured from both spinal fluid specimens.

The features of this case which, in retrospect, helped to differentiate it from those of nonbacterial meningitis were: (a) marked nuchal rigidity (present in only 11 per cent of the cases of ECHO virus), (b) spinal fluid cell count of 2,500 per cubic millimeter (the highest in the cases of viral infection was 1,620 per cubic millimeter) with 91 per cent neutrophils (all patients with ECHO meningitis and more

than 1,000 cells per cubic millimeter had a predominance of lymphocytes), and (c) a cerebrospinal fluid to blood sugar ratio which fell to 19 per cent, a level much lower than that observed in any of the epidemic cases. Any one of these findings alone is compatible with the presence of viral meningitis, but the presence of two or more in the same patient should be highly suggestive of bacterial infection.

While, in the absence of demonstrable bacteria, the spinal fluid cell count and differential and the ratio of sugar to blood glucose are helpful in differentiating bacterial from nonbacterial disease of the meninges, the peripheral white blood count and differential are often without diagnostic significance. As noted above, none of the patients with ECHO virus infection had leukopenia; 44 per cent had total counts above 10,000 per cubic millimeter, and 95 per cent had a predominance of polymorphonuclear leukocytes with 30 per cent showing 80 per cent or more of these cells. These findings emphasize the fact that normal or low total white blood counts with predominance of lymphocytes are not a universal feature of virus infections.

In general, the clinical and laboratory findings in this group of ECHO virus meningitides were quite similar to those described in other epidemics of this disease. The outstanding features were: (a) high incidence of the disease in males and in children under 10 years of age; (b) importance of family contacts in spread of the infection; (c) predominance of headache, fever, nausea, and vomiting; (d) significant incidence of a maculopapular and sometimes petechial rash, especially in children less than 5 years old; (e) frequency of slight nuchal rigidity or its complete absence; (f) scarcity of symptoms of upper respiratory involvement in contrast to the presence of pharyngeal inflammation; (g) infrequency of diarrhea; (h) presence of abdominal pain in children and its absence in adults; (i) the absence of muscle weakness or other irreversible neurologic damage; (j) spinal fluid pleocytosis ranging from 0 to 1,620 cells per cubic millimeter and a predominance of lymphocytes; (k) normal spinal fluid protein in the majority of cases; and (l) high percentage of isolation of type 9 ECHO virus from the spinal fluid.

The following findings are different from or are not mentioned in other reports of this type of meningeal infection: (a) severe nuchal rigidity in only 11 per cent of the patients; (b) abnormally high spinal fluid protein in 7 of 8 adult patients; (c) the absence of leukopenia in the peripheral blood, the frequency of leukocytosis, and the predominance of neutrophils.

Type 9 ECHO virus was definitely proved to be the etiological agent in 70 per cent of the cases; an additional 8 per cent were probably caused by this organism. Insufficient specimens were obtained for adequate viral and serologic study in 12 of the 14 remaining patients. In only 2 instances in which complete investigations were possible was type 9 ECHO virus not implicated. This fact, the inability to demonstrate other viral agents, and the marked similarity of the clinical pictures to those in previously reported outbreaks appear to justify the conclusion that type 9 ECHO virus was the etiological agent in the great majority if not in every one of the cases described in this paper.

CONCLUSIONS

An outbreak of "aseptic" meningitis with a significant incidence of skin eruptions occurred in the Boston area in the summer of 1958. A group of 64 patients, 56 children and 8 adults, was studied. The clinical and laboratory findings were found to be very similar to those reported in previous outbreaks of documented type 9 ECHO virus meningitis. This agent was proved to be the etiological agent in 70 per cent of the cases and of probable significance in an additional 8 per cent.

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RHABDOMYOSARCOMA OF STRIATED MUSCLE ORIGIN IN PREADOLESCENT CHILDREN

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MALIGNANT tumors of striated muscle are rare. The first large series of rhabdomyosarcoma was reported by Rakov[1] in 1937. Stout[2] collected 121 cases in 1946. Pack and Eberhart[3] presented 100 cases in 1952. Davies,[4] Lechner and Moran,[5] Sandison,[6] and Forbes[7] have each reported single cases. In 1957, Arean and Marcial-Rojas[8] described 3 cases of rhabdomyosarcoma in children. In 1958, Caffey and Anderson[9] reported 5 cases, and, in 1959, Moore and Grossi[10] described 37 cases of this neoplasm in children. In all, about 323 cases of rhabdomyosarcoma have been reported; however, only 87 of this number have been found in children. Of these 87 cases, the most common sites of origin of the primary lesion were the head and neck region and the extremities. No attempt has been made to include any discussion of the rhabdomyoma of the heart, myoblastoma, sarcoma botryoides of the vagina in female children, rhabdomyomatous tumors of the male genitals, or rhabdomyoblastic tissue in embryonic renal and hepatic tumors, in teratomas, and in true hamartomas.

It is the purpose of this paper to discuss rhabdomyosarcomas derived from skeletal muscle in children, and to describe 6 additional cases of this tumor occurring in childhood.

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REVIEW OF LITERATURE

Considerations of Pathogenesis.—As judged from the literature, there are no racial, sexual, or geographic factors of significance. These factors, however, are difficult to evaluate accurately because of the small number of cases reported. Trauma of some degree is reportedly present in approximately 11.5 per cent of the cases.[2] However, as no scientific basis exists for a single trauma to a body part as a factor in the pathogenesis of the neoplastic process, this figure of 11.5 per cent should be regarded as insignificant and probably explainable by chance. The fact that a tumor mass is easily traumatized often suggests this as the cause of the tumor to the patient.[9]

Factors of possible causation and pathogenesis that have been mentioned are: (1) rests of embryonic cells with the potential for transformation into neoplastic myoblasts, and (2) malignant transformation in existing mesenchymal tissues.

Prognosis and Treatment.—Primary rhabdomyosarcoma of soft tissue origin has all the usual properties for local invasion and extension. This point is testified to by the high incidence of

local recurrence following excision. The tumor has been shown to have a high rate of metastasis by way of the blood and lymph systems. The site of the metastases judged in the order of reported frequency are: lungs, regional lymph nodes, skin and subcutaneous tissues, pleura, bone, liver, kidney, suprarenal glands, mediastinum, pericardium, pancreas, ovary, and brain.

The treatment of this tumor has consisted principally in simple excision, amputation, and, to a lesser extent, radiotherapy. Often 2 or all 3 methods have been combined. The rhabdomyosarcomas as a group, when treated with radiotherapy alone, have been observed to be radioresistant. However, several writers have postulated that radiation therapy is the treatment of choice for the embryonal type, which is highly malignant and tends to recur rapidly and to metastasize widely. Therefore, it is believed that most of the tumors of this type do not lend themselves to surgical excision. Whether or not maximally tolerated doses of irradiation alone could prove beneficial is as yet undetermined.

Simple excision of the tumor has, in the majority of cases, been followed by local return, metastases, or both. In the cases of local return alone, either further excision or amputation or both have been performed with rather poor results from a curative or survival point of view.

Primary amputation or amputation after biopsy has not bettered the prognosis as much as was originally hoped. The tumor has recurred either in the amputation stump or as metastatic lesions.

As with all malignant neoplasms, it is thought that the earlier it is detected and the more radically it is treated, the better the prognosis. A tumor should never be treated by any method without benefit of biopsy and complete pathologic identification of the tumor type. A small biopsy specimen removed from the tumor will furnish the necessary information and indicate the proper therapy. In the case of rhabdomyosarcoma without evidence of metastases, the treatment should certainly be radical with removal of a large block of surrounding uninvolved tissues. This, of course, may or may not mean amputation.

Microscopic Differential Diagnosis.—Stout[2] states that the tumor cells composed of rhabdomyoblasts are variable in size and shape but usually exhibit one of 3 different shapes: (1) a rounded cell containing a single nucleus, (2) a strap-shaped cell with 2 or more nuclei arranged in tandem, and (3) a racquet-shaped cell with a single rounded nucleus at one expanded end and a tapering body extending outward from this for a variable distance. The cytoplasm is generally acidophilic, sometimes markedly so, and is often granular. If the tissue is properly fixed and stained, either cross-striations, longitudinal myofibrils, or some vague suggestion of their formation may be distinguishable in the majority of tumors. It is usually not easy to find this differentiation (even with ideal preparations), and one must be willing to make a painstaking search under high magnification. The search is rewarding if successful, however, for the diagnosis can then be made with complete assurance. The tumor cells are sometimes vacuolated, and it has been generally accepted that the material in the

vacuoles is glycogen, which was first demonstrated by Marchand in 1885. When there are many vacuoles in cells of giant size, they are sometimes peripherally arranged with delicate cytoplasmic strands separating them and radiating outward from near the nucleus to the capsule. Such cells have been called spider or spider web cells. Since Stout wrote his classic paper, he has added further details, making it possible to classify certain tumors in this category despite an inability to demonstrate cross-striations. It has become increasingly apparent that a number of tumors not fitting his classic description are also undoubted examples of rhabdomyosarcoma.

Horn and Enterline[12, 13] classify this neoplasm into 4 categories or types: (1) pleomorphic, (2) alveolar, (3) embryonal, and (4) botryoid types. The pleomorphic type is the classical form described by Stout in 1946. The alveolar type, resembling adenocarcinoma, contains connective tissue trabeculae with "free" floating cells within the alveoli. The "free" cells may be attached to the alveoli trabeculae by a narrow foot. It is in these "free" cells that myofibrils and cross-striations are seen. The trabeculae, on close examination, are really giant muscle fibers with nuclei in the lateral cytoplasmic extensions, rather than tenuously connected to the main mass of sarcoplasm. The embryonal type, also described by Stobbe and Dargeon,[14] consists of the basic cell types as outlined by Stout. However, these cells are less differentiated and longitudinal and cross-striations may or may not be demonstrated. The botryoid type (not illustrated or discussed here) consists of a multilayered band of cells below the mucus membrane, the so-called "cambrium layer of Nicholson." The cells in this layer are indistinguishable from those of the embryonal type. Longitudinal and cross-striations in the long spindle cells are very difficult to see even with special staining.

The tumors with which the rhabdomyosarcoma are most easily confused are liposarcomas and fibrosarcomas. The liposarcomas commonly form bizarre giant cells but the nuclei are very apt to be pyknotic and lipoid droplets are always to be found in some part of the growth. Fibrosarcoma cells are often elongated and connective tissue fibers are usually present between them. The differential diagnosis of these neoplasms of soft tissue is always a challenge.

CASE REPORTS

CASE 1.—(S. G. H.) F. P. R., a 19-month-old boy, was first seen on July 17, 1957. The mother reported that, 6 weeks before, she had noticed a deformity of the right hip. Since that time, the swelling had become noticeably larger. Weight loss and pallor of the skin were noted although the child appeared bright and alert. The child was referred for definitive diagnosis and treatment. Physical examination 2 days later revealed a tumor mass measuring approximately 10 cm. in diameter in the right gluteal region. There was no limitation of movement of the right hip joint and no pain was experienced with movement or palpation of the tumor.

Roentgenographic studies revealed a tumor of soft tissues approximately 10 by 6 cm. in the right lateral aspect of the pelvis (Figs. 1 and 2) overlying the right iliac bone, extending to the right spinal margin and downward to a point slightly below the greater

femoral trochanter. The outline was smooth and regular. There were no calcifications or striations and the density of the mass (as judged from the roentgenograms) was that of soft tissue. It was similar in all respects to the adjacent striated muscle structure. The bones and the hip joint were not involved. The mother confirmed the swallowing of rocks which were identified as radiopaque masses in the colon. An aspiration biopsy of the gluteal mass was unsuccessful. Roentgenographic examination of the chest showed multiple round, dense shadows in both lung fields and in the hilar areas (Figs. 3 and 4).

Fig. 1.—Posterior-anterior roentgenogram of the rhabdomyosarcoma in the right lateral aspect of the pelvis.

Fig. 2.—Roentgenogram, right lateral view, of the primary gluteal mass found in Case 1.

The child was admitted to the hospital for an open biopsy which revealed tumor tissue of a grayish-red color lying beneath the gluteus maximus muscle.

No treatment of any kind was given. Palliative radiotherapy to the primary hip tumor and the metastatic lung lesions was refused by the parents. The child died at home of his disease 3½ months after the primary mass was first noted. No autopsy was performed.

Pathologic Diagnosis.—The diagnosis was rhabdomyosarcoma, embryonal type, Grade IV (Fig. 5). The several small fragments of tissue removed for microscopic examination showed masses of highly undifferentiated malignant cells grouped around thin-walled blood vessels. There were numerous mitotic figures. The individual cell showed some tendency to be elongated with suggested oval forms and to be arranged in parallel and sweeping formations. A similarity to rhabdomyoblasts was noted but no cross-striations were identified. Although tumor cells intermingled with strands of striated muscle showing varying degrees of degeneration demonstrated a few myofibrils, a transition from one to the other could not unequivocally be identified.

Summary.—This highly malignant neoplasm in a 19-month-old child caused the death of the patient 2 months following clinical diagnosis. The tumor was classified as an embryonal type of rhabdomyosarcoma, primary in the gluteus maximus with metastatic lesions in the lungs.

Case 2.—(T. C. H.) K. D. H., a six-year-old white girl, was first seen by

Fig. 3.

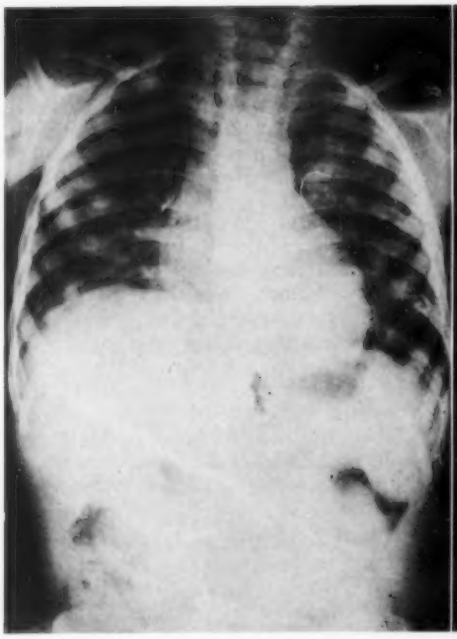

Fig. 4.

Fig. 3.—Roentgenographic demonstration of the metastatic lesions in the lungs in Case 1.
Fig. 4.—Lateral roentgenogram showing multiple round, dense shadows in lung field.

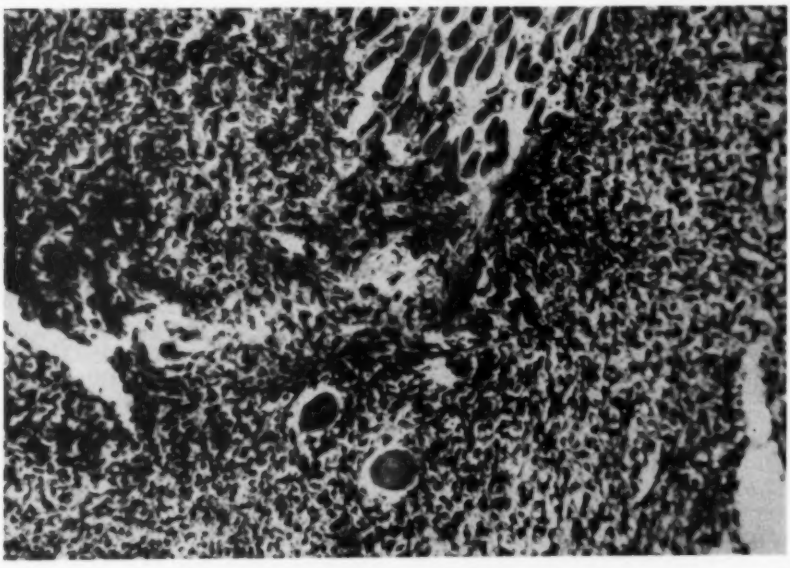

Fig. 5.—Microscopic appearance of the tumor in Case 1.

a physician in 1952 because of a lesion on the mucosal surface of the left ala of the nose. This was removed by currettage but apparently not examined microscopically. Four months later, a neoplasm was encountered in the left maxillary sinus. On microscopic examination at the time of admission to the hospital this tumor was interpreted as being a highly malignant sarcoma. The patient was treated with radiotherapy at that time with clinical regression of the tumor.

after a final admission to the hospital, there was a sudden increase in the dyspnea and cyanosis, which was followed by coma and death.

The final clinical diagnosis was lymphosarcoma of the nasopharynx with metastases to the lungs.

Postmortem Examination.—The significant findings were as follows: there was a large, firm, lobulated, and fairly well-demarcated mass measuring 15 by 10 by 10 cm. within the right lung and

Fig. 6.—Case 2. Gross specimen showing the cut surface of the right lung. Note large discrete metastatic nodule of the tumor protruding from the cut surface. Areas of necrosis with formation of small cysts are visible.

Six months after the appearance of the initial lesion, nodules appeared in the back and there were roentgenographic evidences of metastases to both lungs. Twenty-one months later roentgenographic evidence of metastases to the distal end of the femur was noted. Radiotherapy again produced slight response. One month before death, respiration became difficult and subjective complaints of defects in visual perception were recorded. The only therapy given at this time was irradiation to the right femur. Shortly

occupying the major portion of the lower and middle lobes. On the cut surface, the substance of the mass extended above the level of the surrounding lung (Fig. 6). There was extensive hemorrhage and necrosis and a few small cystic spaces were identified within the tissue. There was evidence of extension of the neoplasm into the right main stem bronchus which then extended proximally toward the carina (Fig. 7). In addition, there was invasion of the right main pulmonary vein and extension into the left atrium.

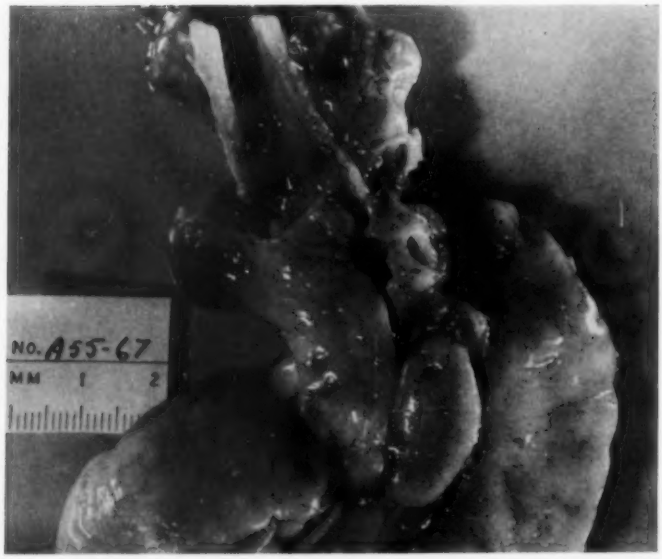

Fig. 7.—Case 2. Gross appearance of the neoplastic growth in the right main stem bronchus.

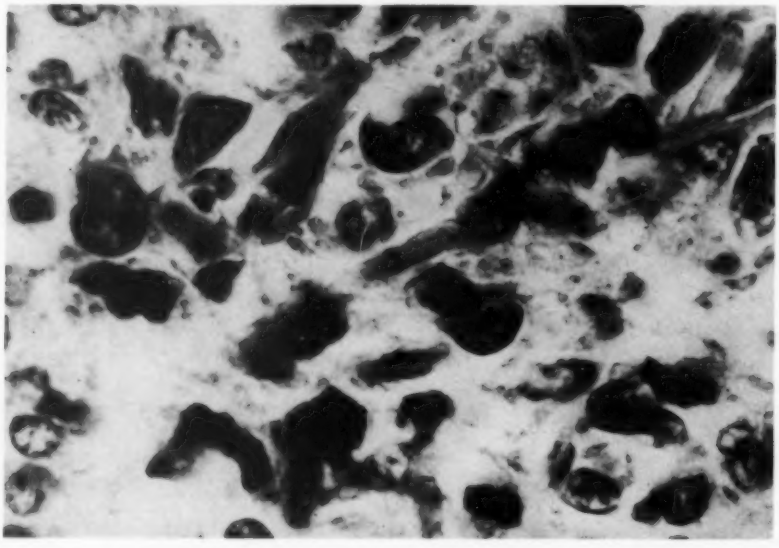

Fig. 8.—Photomicrograph illustrating the metastatic lesions found in the lungs in Case 2. Note the cross-striations within the elongated neoplastic cells.

A similar nodule but of smaller size, measuring 8 cm. in maximum diameter, was present in the left lower lobe. The tumor had invaded the left pulmonary vein and also had extended into the left atrium as a discrete mass. The mesenteric and mediastinal nodes were enlarged. As far as could be ascertained from the gross appearance, it appeared that the nodes contained tumor.

Microscopic Description of the Tumor.—There was a marked pleomorphism of the tumor cells with numerous large, multinucleated forms varying from round to elongated spindle forms. In many of the cells, cross-striations were identified, establishing the diagnosis as rhabdomyosarcoma (Fig. 8).

Final Anatomical Diagnosis.—(1) Rhabdomyosarcoma, Grade III; (a) (?) primary in the maxillary sinus, (b) metastatic rhabdomyosarcoma in the lungs, femur, and mediastinal and bronchial lymph nodes, and (c) tumor thrombus in the pulmonary veins; (2) bronchopneumonia, bilateral; (3) focal atelectasis.

Summary.—A 6-year-old girl died of a rhabdomyosarcoma believed to be primary in the nasal cavity with widespread metastases 3 years following the first clinical manifestations of the disease.

CASE 3.—(M. D. A. H.) C. A. W., a 20-month-old girl, was first seen by a physician on July 7, 1955. The mother stated that, while bathing the baby that morning, she had noticed a lump underneath the right arm. This lump was soft, white, and approximately the size of the mother's thumb. There seemed to be no pain associated with pressure or with movement of the right arm. The patient was admitted to a local hospital where the lesion was excised under ether anesthesia. The pathologic diagnosis of the biopsy material, which was confirmed by a second pathologist, was "rhabdomyosarcoma."

Nine days later the patient was admitted to the hospital for further care. Physical examination was essentially negative except for one shotty, freely movable lymph node in the right supraclavicular area and one 5 mm. node in the right anterior cervical chain. A discrete, freely movable lymph node was found in the left supraclavicular area and several such nodes were present in the left lateral and posterior and cervical chains.

Roentgenographic survey of the chest, skull, and extremities was negative, showing no evidence of metastases. Urograms, complete blood studies, and urinalysis were not regarded as significant and were generally within normal range.

A right forequarter amputation was performed with dissection of the right axillary and right supraclavicular lymph nodes. The postoperative course was uneventful and the patient was discharged from the hospital 10 days later.

The patient has been followed at 6 month intervals in the clinic. At the present time, 2½ years following operation, no clinically manifest recurrences have been noted.

Summary of Pathologic Findings.—The tumor removed in the original biopsy measured 1.5 by 1.5 by 2 cm. On cut section the surface showed an admixture of dark brown, red, and white streaked connective tissue–like material. No apparent capsule was noted.

Sections prepared for microscopic study revealed tumor cells which for the most part were small, round, or oval and often looked like lymphocytes and seemed to show very little cytoplasm. In other areas the cells, while still showing the same nucleus, contained more cytoplasm. Some of these cells were elongated and showed intracellular myofibrils with definite cross-striations. In still other areas the tumor cells were slightly larger and contained a more voluminous

amount of eosinophilic granular cytoplasm. These cells were round to oval shaped and the nuclei acentrically placed. Mitotic figures were numerous throughout the sections taken.

The pathologic diagnosis was rhabdomyosarcoma, Grade III, primary in the soft tissue of the right arm (Figs. 9 and 10).

The operative specimen consisted of the right arm, the right scapula and the lateral third of the right clavicle. On the medial aspect of the skin of the upper arm, extending into the axilla, a longitudinal scar measuring 4.7 cm. in length was noted. Underneath the distal end of the scar among unidentified muscles, 2 rather firm and almost nodular grayish-white lesions measuring 3 and 5 mm. in diameter were prepared for microscopic study. Another suspicious, rather firm, grayish-white lesion found at the distal end of the scar was submitted for microscopic examination together with fragments of the surrounding vessels and muscles. Twenty-five axillary lymph nodes and 6 supraclavicular lymph nodes were recovered and sectioned.

In none of the many sections taken at the primary site of previous excision or from the lymph nodes recovered was there any tumor demonstrated.

Final Pathologic Diagnosis.—(1) Rhabdomyosarcoma, Grade III (section from the original excisional biopsy); (2) no tumor demonstrated in the tissues removed from the forequarter amputation.

Summary.—This malignant neoplasm of a 20-month-old child, classified as a rhabdomyosarcoma, has shown no clinical or roentgenologic evidence of return 2½ years following radical operation.

CASE 4.—(T. C. H.) J. M. P., a three-year-old girl, was first seen by a physician in October, 1958, with the chief complaints of difficulty in breathing, some difficulty in swallowing, and gagging on solid food. The diagnosis of croup was made at that time. However, several days later, because of increasing respiratory difficulty, an emergency tracheotomy was performed. The laryngeal obstruction was found to be due to a tumor. Microscopic examination of a biopsy specimen at that time revealed rhabdomyosarcoma of the larynx. Physical examination revealed a tumor mass either attached to the epiglottis or displacing it.

Roentgenographic studies of the neck demonstrated a mass in the posterior pharynx approximately 3 cm. in diameter. Direct laryngoscopy was performed to locate and to determine the extent of the mass and the type of operation necessary for definitive treatment. The epiglottis was found to be entirely free and pushed forward by the mass which filled the entire hypopharynx. The tumor appeared to originate from the region of the posterior commissure on the postcricoidal area. The tumor extended to the false cord and epiglottic fold on the left. The tumor surface was slightly ulcerated on the left and bled easily. The right piriform sinus appeared normal. No biopsy was taken at this time.

Preoperative roentgenographic bone survey and chest films revealed no evidence of metastatic lesions. All clinical laboratory studies were within normal limits.

Block laryngectomy was performed including the hyoid bone, muscles, and larynx. The postoperative course was complicated by a wound infection and fistula formation which was treated with drainage and antibiotics.

The patient has been followed at monthly intervals. At the present time, 6 months following operation, no clinically or roentgenologically manifest recurrences have been noted.

Pathologic Diagnosis.—Rhabdomyosarcoma, Grade III. Microscopic sections of the specimen revealed a large, fairly well-localized and apparently encapsulated tumor mass partially covered by a thin layer of normal

Fig. 9.

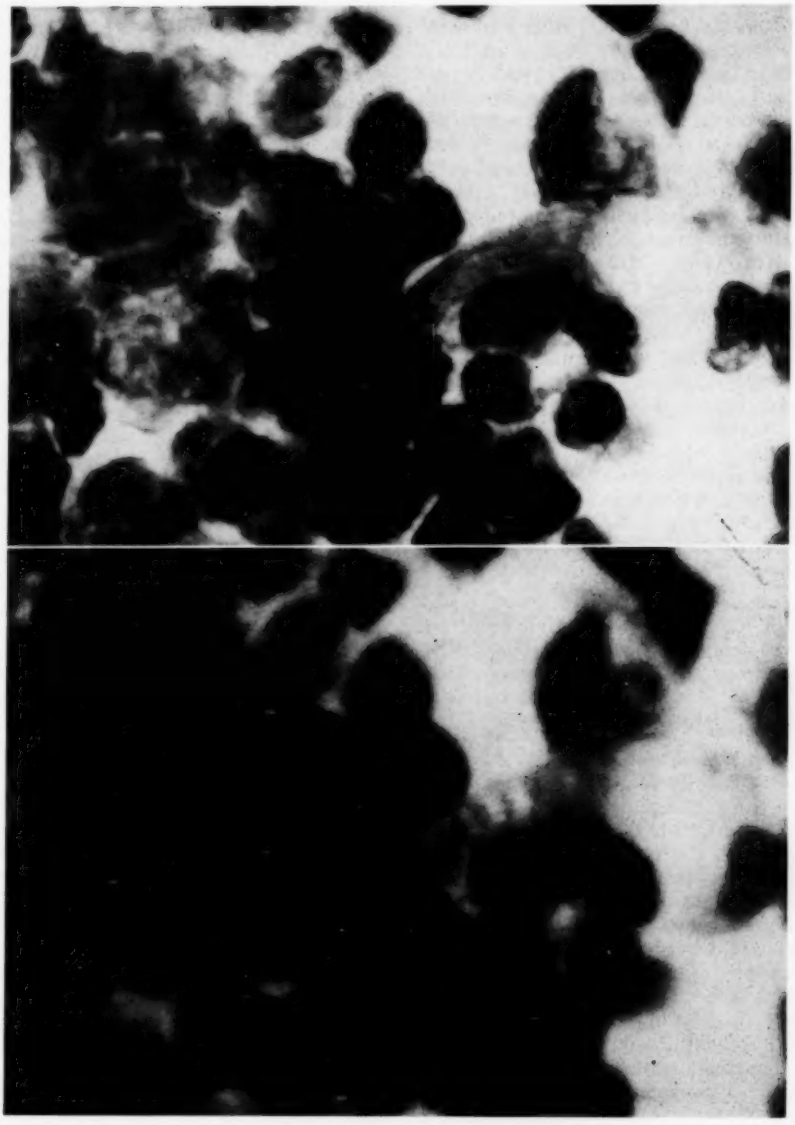

Fig. 10.

Fig. 9.—Photomicrograph demonstrating the rhabdomyosarcoma found in Case 3.
Fig. 10.—Case 3. Photomicrograph illustrating cross-striations with polarized light.

stratified squamous epithelium. Over a large area, this epithelium has been eroded, and a fibrinopurulent exudate containing numerous bacterial colonies was found.

The tumor cells were poorly arranged in an ill-defined lobulated, loose, vascular stroma. Pleomorphism was marked. Most of the nuclei were large and occasionally indented with a poorly defined cytoplasm. Occasional cells were encountered with elongated streamers of cytoplasm and in a rare one of these cells, striations were definitely identified. Multinucleated and giant cell forms were abundant. Mitoses were prominent.

The capsule formed of compressed connective tissue was intact, although it was found to be only a few microns in thickness in several areas. No definite evidence of extension of the tumor through this capsule was found.

Microscopic sections of the cricoid cartilage, epiglottis, muscles attached to the hyoid bone, and a single lymph node showed no evidence of tumor.

Summary.—This malignant neoplasm in a 3-year-old child, identified as a rhabdomyosarcoma of the larynx, has shown no clinical or roentgenologic evidence of return 6 months following radical operation.

CASE 5.—(T. C. H.) D. W. J., a 3½-year-old white boy, was first seen with the chief complaints of a drooping left eyelid with slight injection of the "white of the eye" and some "wateriness" of approximately 2 to 3 weeks' duration. A diagnosis of allergic conjunctivitis was made. The patient was treated with antihistamines for 2 days with no improvement. Re-evaluation of the patient revealed a firm, palpable mass above the left orbit and ptosis with some fullness of the left eyelid. The extraocular movements, pupil size, and reactions to light and accommodation were within normal limits. The remainder of the neurologic examination revealed no signs of intracranial lesion. The impression at that time was an orbital tumor.

Roentgenographic films of the skull demonstrated no bony abnormalities around either the orbit or the optic foramen. Bone survey and chest films were negative for metastatic disease. Clinical laboratory tests were all within normal limits except for an elevated white blood count with an increase in lymphocytes.

At operation, an encapsulated mass in the upper temporal quadrant of the left orbit was found. A complete exenteration by block method was carried out. The orbital defect was closed with a split thickness skin graft obtained from the abdominal wall.

The postoperative course was uneventful and the patient was discharged from the hospital 10 days later.

Pathologic Findings.—Microscopic examination of a frozen section at the time of operation revealed only a malignant tumor of unknown type. Further study of multiple permanent sections demonstrated rhabdomyosarcoma, Grade III. The tumor was localized but poorly circumscribed and only partially encapsulated. It extended into the lacrimal gland and was bordered on one edge by a thin strip of striated muscle. The cellular structure was highly pleomorphic with individual cells present irregularly in poorly defined clusters. There was marked variation in size and shape with numerous large multinucleated and multilobed forms. Few pyknotic cells and occasional mitoses were noted. The cytoplasm was generally indistinct but abundant and finely granular. Occasional forms with long streamers of cytoplasm contained indistinct striations. The tumor extended to, but not into, the striated muscle. There was direct extension into the lacrimal glands. Examination of the soft tissue contents of the orbit was negative for tumor cells.

Summary.—A malignant neoplasm found in a 3½-year-old child and classified as a rhabdomyosarcoma of the lacrimal gland has shown no clinical or roentgenologic evidence of recurrence 5 months following radical operation.

CASE 6.—(T. C. H.) R. R. H., a 4-year-old white boy, was first seen by a physician 8 weeks prior to the first hospitalization for an ulcerated area on the anterior surface of the uvula. This lesion responded poorly to therapy but eventually cleared. Four weeks later, an enlargement and papillomatous lesion of the uvula developed. On the first admission to the hospital, the chief complaints were: (1) vomiting of one week's duration which on occasions was described as projectile in character; (2) inability to see out of the right eye, and (3) stumbling for the past 2 to 3 weeks. The patient had also complained of generalized headaches for the past 3 to 4 months.

Eye examination under anesthesia revealed marked papilledema, 5 to 6 diopters, with considerable edema of the retina, although no hemorrhage or exudate was present. The deep tendon reflexes were hypoactive and the child had a broad-based gait. There was no sensory defect present.

Ventriculograms demonstrated a large lesion in the posterior portion of the left parietal lobe with displacement of the ventricular system to the right.

Surgical excision of the papillary lesion of the uvula was performed. The pathologic diagnosis of this excisional biopsy was rhabdomyosarcoma. The patient also underwent a craniotomy. A huge neoplastic lesion which had almost entirely destroyed the left hemisphere was found and excised. The pathologic interpretation stated that this lesion was a highly anaplastic malignant lesion most likely of teratomatous origin.

The patient's postoperative course was uneventful and he was discharged from the hospital 3 weeks after operation.

Although completely blind, the child did well for 6 weeks and was able to walk in spite of a partial right hemiparesis. At that time, he had meningitis which was effectively treated with antibiotics. Following the meningitis, he began to have seizures. These were controlled with phenobarbital and Dilantin. Just prior to readmission to the hospital, he began to take food poorly, began vomiting, and became dehydrated. The skull was enlarged and bulging along the old incision scar and burr holes in the left temporal area. The right arm was almost paralyzed.

A second burr hole craniotomy revealed a massive recurrence of the firm vascular tumor which had been removed 2 months earlier. The tumor had grown to almost its original bulk. The patient showed slight improvement immediately postoperatively but began to go downhill rapidly, became semicomatose, and continued to have seizures until his death 3 months after the onset of symptoms.

Summary of Pathologic Findings.—The papillomatous lesion of the uvula was an ovoid mass measuring 3.0 by 1.2 by 0.5 cm. It was made up of many translucent lobules varying from 0.4 to 0.8 cm. in diameter.

Microscopically, the lesion was described as follows: arising from the submucosa there was a cellular pleomorphic tissue which had grown in a polypoid pattern extending outward with an almost complete covering of stratified squamous epithelium. The cellularity of the lesion was varied, demonstrating both dense and loose arrangement of cells, which showed marked pleomorphism. In some of the larger cells with streamers of cytoplasm, indistinct striations were identified. The overlying epithelium was intact in all areas; however, the tumor extended laterally beneath the epithelium of the soft palate.

Microscopic sections from the brain lesion and from the lymph nodes of the neck, in general, demonstrated the same marked pleomorphism. Mitoses were abundant. Occasional cells with long, streaming cytoplasm and huge, bizarre multilobed and multinucleated cells were seen. There were many elements which resembled rhabdomyosarcoma, although striations were identified only in the hematoxylin and

eosin preparations. A Phosphotungistic acid hemotoxylin stain did not demonstrate any cross-striations.

Final Pathologic Diagnosis.—Diagnosis was rhabdomyosarcoma, embryonal type, Grade IV, with metastases to the lymph nodes of the neck and to the brain.

Summary.—A 4-year-old boy died of a rhabdomyosarcoma believed to be primary in the uvula with metastases to the brain and cervical lymph nodes 3 months following the first clinical manifestations of the disease.

DISCUSSION

These 6 cases are all examples of rhabdomyosarcoma of soft tissue origin occurring in preadolescent individuals. Variation in the tumor differentiation believed to be important to some extent in affecting prognosis was noted. In Cases 1 and 6, the tumor was highly anaplastic, and, although some differentiation occurred, much of the growth was bizarre and showed little resemblance to myocytes. In Cases 2, 3, 4, and 5, the tumor recapitulated the development of skeletal muscle much more realistically. Even the least differentiated cells were not as embryonal as in Cases 1 and 6. The growth of the tumor in the lung in Case 2 demonstrated these levels of differentiation especially well.

Treatment as given in these 6 cases in relation to the generally accepted therapy for this disease was, in the author's opinion, adequate in all cases. The fact that no treatment was given in Case 1 did not mean that the patient did not receive careful evaluation. Of the 3 types of treatment now available, the one which could have been used was radiotherapy for palliative purposes only. It was questionable that any regression would have been obtained in view of the rapid growth of the primary neoplasm and the extensive lung metastases. In Case 2, where irradiation was used exclusively because of the surgical inaccessibility of the primary lesion, some remission was obtained. However, as has been reported, when the tumor returned in the primary site and as metastases, it was highly radioresistant and regression was minimal. In Cases 3, 4, and 5, the treatment consisted of radical operation with forequarter resection, block laryngectomy, and exenteration of the orbit, respectively. In addition to the amputation of the right arm and scapula with the axillary lymph nodes, in Case 3, the supraclavicular lymph nodes were also removed. Pathologic study of the tissues showed no tumor at the primary site or in the regional lymph nodes. The prognosis at the time of operation was infinitely better than in Cases 1, 2, and 6. Now, 2½ years postoperatively, there is no clinical evidence of return of the disease in the lungs or in the amputation stump. Although it is still too early to be certain of the final outcome of this patient, it is fair to assume that recurrence of the disease is not likely. In Cases 4 and 5, neither local nor distant metastases could be demonstrated by either pathologic study of the tissues or roentgen-ray surveys. As in Case 3, it is still much too early to predict the outcome of these 2 patients, since only 5 and 6 months, respectively, have elapsed since operation. Their prognosis, however, is better at the time of operation than that in Cases 1 and 6.

Although radical operation was used in Case 6, it was only palliative in its effect on the final disposition of the patient. The tumor had already metastasized to the brain, probably by direct extension, before the patient was ever seen by a physician. The prognosis of this patient at the time of operation was extremely poor.

It has been possible to apply histologic grading to rhabdomyosarcoma, but because most of the tumors were classified as Grade III or Grade IV, the significance of grading in the selection of therapy has been of little import. A possible application of the usefulness of grading was found in the 6 cases reported here. In Case 1, in which the pathologic diagnosis was rhabdomyosarcoma, embryonal type, Grade IV, numerous metastatic lesions were present in the lungs at the time of diagnosis although it had been only approximately 6 weeks before that there was an abnormal growth noted on the patient's right hip. The highly malignant neoplasm of Case 6, also diagnosed as embryonal type, Grade IV, demonstrated extensive cerebral metastases at the time of diagnosis even though clinical symptoms had been present for only 8 weeks. In Cases 2, 3, 4, and 5, the neoplasm was classified as Grade III. This tumor, showing more differentiation of its cells, invades and spreads less rapidly, which may offer some explanation for the more favorable response to the roentgen therapy given in Case 2, and which was believed to have slightly increased the survival time. The tumors in Cases 3, 4, and 5 did not produce local, regional, or distant metastases as could be judged from the examination of the tissue removed and the postoperative period of freedom from recurrence. It may be assumed, therefore, in Case 3, that the radical excision of this tumor with absence of demonstrable metastatic lesions, and the presently observed long survival period, strongly indicate a possible cure of the disease. In Cases 4 and 5, although treated by radical excision of the primary tumor with no demonstrable metastases found at operation, the postoperative periods have not been of sufficient length, as yet, to warrant a prognosis as to possible cure.

SUMMARY

Six cases of rhabdomyosarcoma of striated muscle origin (soft tissue origin) in preadolescent children are reported and the literature reviewed. Three of the patients died in 2 months, 3 months, and 3 years, respectively, following clinically manifest disease. One patient, treated by forequarter amputation, is living, well, and clinically free of disease 2½ years following the first clinical manifestation. Two other patients, treated by radical operation, are also living, well, and free of disease 5 and 6 months postoperatively.

Rhabdomyosarcoma of striated muscle origin continues to be a rare and catastrophic disease of childhood. Early detection with immediate application of therapy is considered to be the only hope of preventing metastases and obtaining a cure. Biopsy is thought to be the most important single aid to early recognition. As with most types of cancer, close cooperation among the surgeon, the pediatrician, and the pathologist concerned with the diagnosis and treatment of the disease is necessary.

The accepted therapy is radical operation with removal of a large block of surrounding uninvolved tissues and amputation of the total part where possible and clinically deemed necessary. Roentgen therapy may be tried as a palliative measure in surgically inaccessible tumors, or in the metastases from previously excised primary neoplasms.

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CONGENITAL NEUROCUTANEOUS SYNDROMES OF CHILDHOOD

III. Sturge-Weber Disease

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THE classical clinical picture of Sturge-Weber disease is characterized by: (1) vascular nevi (port-wine stain) on the face, (2) convulsions often focal and contralateral, (3) hemiparesis and occasionally homonymous hemianopia contralateral to the facial lesion, (4) ipsilateral intracranial calcification, and (5) varying degrees of mental retardation and behavior disturbance.

The neurologic findings are due to degeneration of the cerebral cortex secondary to the vascular anomaly in the meninges on the same side as the facial lesion. At times the vascular abnormality may involve the ocular choroid and lead to glaucoma. Involvement of the viscera may occur but is usually asymptomatic.

Eight patients with this disease have been seen at our clinic. One patient presented a "hybrid" picture of this disease. Several cases exhibited certain interesting features. Histopathologic studies of the surgical specimen of brain removed from one of our patients were made by Dr. E. C. Alvord, Jr., and his findings are included.

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HISTORICAL

The coexistence of facial nevus and buphthalmos was first noticed by Shirmer[1] in 1860. Sturge,[2] in 1879, reported a similar case with focal seizures on the side opposite to the facial nevus. He predicted that there must be a vascular anomaly on the same side of the brain as the one on the face. Kalischer, in 1897,[3] and 1901,[4] demonstrated an extensive angioma involving the cranial bones and the soft meninges in a 1½-year-old child but he did not observe calcification either in the gross or microscopic examination of the brain. We now know that calcification is generally not present in infancy.

In 1906, Cushing[5] operated on 2 patients with facial vascular nevi with convulsions and hemiparesis. He found marked vascularization of the skull and dura mater on the side of the facial nevus. The vascular lesions followed the distribution of the trigeminal nerve on the face, on the scalp, and even in the dura mater.

Hebold,[6] in 1913, noted for the first time the deposition of calcium in the brain upon gross examination at autopsy. Volland[7] in the same year demonstrated intracerebral calcification microscopically. Weber,[8] in 1922, reported a case with bilateral facial

nevus more extensive on the left side. Roentgenograms of the skull revealed greater opacity of the left half of the cranium. Re-examination of the skull 7 years later (1929)[9] demonstrated the wavy, double contoured calcification characteristic of this condition. Such calcification was first described by Dimitri,[10] in 1923; he thought it represented calcified blood vessels. By careful postmortem examination of a patient in whom intracranial calcification was demonstrated before death, Krabbe[11, 12] found that the *calcium was in the cerebral cortex* and that the wavy appearance of the calcification corresponded to the contour of the cerebral gyri and sulci.

ETIOLOGY

The available genealogic investigations of Sturge-Weber disease suggest an irregular dominant inheritance.[13] It has been said that the occurrence of the disease in twins of unaffected parents is suggestive of recessive inheritance but re-examination of the cases cited by Refsum[13] shows that these were not truly cases of Sturge-Weber disease.[14]

The complete syndrome has rarely been reported in more than one member of the same family. Abnormal skin manifestations are, however, not uncommon among family members of Sturge-Weber patients.

PATHOLOGY

The basic pathology of Sturge-Weber disease is a vascular malformation, angiomatosis, affecting primarily the nervous tissue and other body tissues wherever mesenchymal derivatives occur. Thus, involvement of the lungs, the gastrointestinal tract, and the ovary have been reported.[15]

On the face, the characteristic nevus may be unilateral or bilateral. The correlation between the distribution of the vascular lesion and the sensory divisions of the trigeminal nerve was first noted by Cushing.[5] Nevoid lesions may be present on the scalp, skin of the neck, trunk, and extremities. These lesions usually follow the radicular distribution of cerebrospinal nerves, although the conformation may not be exact. Overlap of several dermatomes is not uncommon.[16]

Of clinical importance are the pathologic changes in the brain which give rise to neurologic symptoms. Some recent investigators[15, 17] believe that the changes in the brain are secondary to the vascular malformation in the leptomeninges. They did not find true angioma in the brain proper. A recent report by Roizin and co-workers[18] indicated that angiomatous changes were found in the gray and the white matter of the brain.

Grossly circumscribed foci of meningeal thickening, rich in dilated veins, are found most commonly in the occipital pole, but they may be found over the other lobes of the brain. Increased vascularitiy is also found in the cortical and subcortical regions. The affected part of the cerebral cortex is atrophic and sclerotic. There are loss of neurons and fibers, extensive gliosis, pericapillary fibrosis, and deposition of calcium and iron compounds in the capillary walls and in the cortical parenchyma. The cortical calcification follows cerebral convolutions and is characteristically demonstrated in roentgenograms of the skull as double curvilinear densities. These deposits as well as the atrophic changes may not be demonstrated in

the very young but increase as the patient grows older. These changes are not limited to any particular layer of the cerebral cortex but occur most prominently in the middle of the cortex.

Unrelated to the angiomatous malformation, Wohlwill and Yakovlev[15] described scattered anomalies of the cytoarchitecture both in the central and the peripheral nervous systems. These anomalies consist of failure of migration of neuroblasts to their normal destination, for example, the presence of neurons in the leptomeninges. The authors designated this process as "ectopia." In examining the Gasserian ganglia in 2 of their 4 patients, they found these to be larger than normal because of proliferation of capsular cells. These changes are believed to represent malformation of the various derivatives of the neural crest.

The vascular anomaly may also involve the conjunctiva, oral and nasal mucosa, and the choroid of the eye. Involvement of the choroid is an important factor in producing buphthalmos.[19]

In addition to the primary pathologic changes described above, a number of other congenital malformations have been found in Sturge-Weber patients. Abnormalities of the eyes other than buphthalmos, such as heterochromia iridis and coloboma, have been observed. In one of our patients (Case 7) coaretation of the aorta, a highly arched palate and abnormally developed ears were present.

PATHOGENESIS

The basic mechanism of the angiomatous malformation is not well known. Certain speculations and theories may be briefly summarized. The correlation between the distribution of the sensory branches of the trigeminal nerve and that of the facial nevus has been noted. To account for the angiomatous growth in the skin of the face, scalp, and meninges, and the lack of involvement of the brain per se, Cushing and Bailey[20] believed that the anomaly must arise in a very early stage during the development of craniocerebral vascularization in the embryo.

Streeter[21] divided the development of cerebral vascularization into 5 stages: (1) at first, the primordial vascular plexus is established; (2) this slowly differentiates into arteries, veins, and capillaries; (3) as the dura and cranium develop, the vascular system breaks up into a superficial bed supplying the face, scalp, meninges, and the choroid and a deep bed supplying the brain; (4) adjustment of vascular channels to growth and differentiation of the ear and the brain occurs next; (5) maturation of the arteries and veins is the final stage.

It was suggested[20] that during the third stage a maldevelopment of a vascular area in the superficial bed might lead to vascular nevus of the skin of the face, the meninges, and the choroid.

Wohlwill and Yakovlev[15] postulated that maldevelopment such as hyperplasia of capsule cells of the Gasserian ganglia were due to disturbed migration of neuroblasts from the neural crest.

The first branch of the trigeminal nerve and the occipital region of the brain are by far the most frequently affected. In a study of 36 cases collected from the literature Kautzky[22]

demonstrated a close association between the distribution of the facial nevi with meningeal angiomatosis; thus, a nevus of ophthalmic distribution is generally associated with an occipital lesion, one of maxillary distribution with parietal lesions, and one involving all 3 divisions of the trigeminal nerve with lesions of the entire hemisphere. These data led Kautzky to conclude that the skin of the face and the meningeal coverings of the cerebral hemisphere represent metameric units in relation to the 3 sensory divisions of the trigeminal nerve which innervate the mesodermal derivatives of the corresponding branchial arches. The ophthalmic division (first branchial arch) innervates the meninges of the occipital lobe, the latter becoming displaced posteriorly during the development of the cerebral hemisphere. Kautzky also advanced the hypothesis that developmental defects in vasomotor innervation to the malformed blood vessels in Sturge-Weber disease may be additional factors causing their dilatation and hyperplasia.

SYMPTOMATOLOGY

The cutaneous lesions are present at birth. The localization and extent of the cerebral anomaly determine the severity of the clinical picture. Not all of the classical symptoms and signs are present in every case. The cerebral symptoms usually make their first appearance in infancy. The initial symptom is either a convulsion or hemiparesis. Other functional disturbances, such as slow development and behavior problems, may appear later.

Age of Onset of Neurologic Symptoms.—In most instances neurologic symptoms begin in infancy. This has been true in 8 of our cases, Case 9 being an exception. Focal or generalized convulsions are the most common, and motor weakness is the next most common symptom. These observations are summarized in Table I.

Nevi.—The skin lesions or port-wine stains are present at birth in all cases (Table I). They are sharply demarcated and usually are not elevated. The color varies from pink to purplish red and fades on pressure.

The extent of the skin nevi is not always indicative of, or proportional to, the severity of the neurologic symptoms. In Case 3 of our series the facial nevus is minimal, yet the seizures are most protracted, and mentality and behavior are severely affected. Neither is the facial nevus always a reliable indicator of the site of the cerebral lesion. Thus, the patient in Case 1 in our series has a small facial nevus on the right side, has right-sided seizures, and shows hemiparesis and hemiatrophy in the right arm. This patient might have bilateral cerebral vascular anomalies with the predominant lesion on the *left* side. The demonstration of high voltage focal spike and wave activity in the *left* occipital and the *right* temporal regions in 2 electroencephalograms substantiates the assumption of bilateral lesions.

Convulsions.—Convulsions are the most striking symptoms (Table II). Lund,[23] in 1943, reviewed 144 reported cases and found that 81 patients (56 per cent) had convulsions and 43 patients (30 per cent) had paresis. All but one of our patients had seizures. Focal motor seizures are by far the most common type. Generalized convulsions are less frequent. Psychomotor seizures are occasionally seen.

TABLE I. CLINICAL DATA OF PATIENTS WITH STURGE-WEBER DISEASE

CASE	PATIENT	AGE WHEN FIRST SEEN	INITIAL SYMPTOM	AGE AT ONSET OF INITIAL SYMPTOM	CUTANEOUS FINDINGS	NEUROLOGIC FINDINGS
1	M. H.	2½ yr.	Weakness, right arm	7 mo.	Facial nevus, right 2nd	Hemiparesis and atrophy, right arm
2	K. M.	3 11/12 yr.	Seizure, left	4 mo.	Facial nevus, right 1st and 2nd	Hemiparesis and atrophy, left side; nystagmus, right eye
3	W. B.	7 mo.	Seizure, right	5 mo.	Facial nevus, left 1st	Hemiparesis and atrophy, right; hemianopia, right
4	R. D.	5 yr.	Seizure, right	4 mo.	Facial nevus, left and right; left upper chest and left arm nevi	Hemiparesis and atrophy, right; glaucoma, left eye (at 7 yr.)
5	S. P.	7 yr.	Seizure, generalized	5 mo.	Facial nevus, right; scattered left; right upper chest; right leg and foot	Knee jerks 3 plus
6	T. S.	3 11/12 yr.	Seizure, left	2 mo.	Facial, left and right	Buphthalmus, left; coloboma, left; microcephaly
7	B. R.	1 yr.	Seizure, right	2 mo.	Facial left; head and neck, left; left buttocks; leg and foot	Hemiparesis and atrophy, left; hemianopia, left
8	Y. P.	13 mo.	Seizure, tonic	3 mo.	Facial, left 1st branch	Slight hemiparesis, right
9	R. A.	6½ yr.	Gastrointestinal bleeding	3 yr.	Facial, both sides scattered. Also trunk and legs	Hemiparesis, right; buphthalmus, bilateral

Massive spasms or myoclonic and akinetic seizures have not been reported in Sturge-Weber disease. This is in sharp contrast with tuberous sclerosis in which the latter seizure patterns are the most common.

Motor Deficit.—Hemiparesis and hemiatrophy occur less frequently than seizures. As a rule the involvement is contralateral to the facial lesion. The paretic limb (or limbs) often shows less than normal growth. Some cases are surprisingly free of motor deficit or indeed of any neurologic abnormality.

Disturbance of Mentality, Behavior, and Speech.—The degree of these functional disturbances varies widely from patient to patient. In our series (Table III) 7 children were of school age; only 2 were in regular classes in public school (Cases 1 and 9). One patient (Case 4; I.Q. 60 to 70) was in a special class. The mentality of the others was too deficient for them to benefit from schooling. Three of these patients were quite unaware of their surroundings; 2 never developed speech; 1 could say only one word, "Mama."

The degree and extent of cerebral calcification increases with time, but there is no consistent correlation between the extent or degree of calcification and neurologic abnormality.

Ocular Manifestations.—Two of our 9 patients had buphthalmos at birth. One was unilateral (Case 6), involving

TABLE II. SEIZURES AND EEG DATA IN PATIENTS WITH STURGE-WEBER DISEASE

CASE	AGE AT ONSET	INITIAL SEIZURE AND COURSE	ELECTROENCEPHALOGRAMS	FAMILY HISTORY
1	7 mo.	Right-sided seizures at first visit when 2½ yrs. of age; gradual reduction of seizures. Last seen at 6½ yrs.	5½ yr.—Hyperventilated continuous spike, slow wave in left occipital area 6½ yr.—Same	Mother's left pupil greater than right; iris colors are different
2	4 mo.	Left-sided seizure at 4 mo. of age, continued; later generalized shaking and limpness until hemispherectomy in 1954	9 mo.—Depressed activity right side 3 9/12 yr. — Hyperventilated sharp and slow wave right F.	Maternal aunt and uncle had hemangiomas on arm at birth
3	7 mo.	Right-sided seizures until surgical resection in April, 1957	7 mo.—Depressed activity, left side 4 yr.—Same, plus sharp and slow wave focus in left occipital-temporal region 5 9/12 yr.—Same as above plus generalized slowing 5 8/12 yr. — Postoperative-depressed activity left, but no focal epileptiform activity	Negative
4	4 mo.	Right-sided seizure, then left sided, then generalized. Last seen June, 1958	5 2/12 yr.—Diffuse slow depressed activity left occipital region 9 3/12 yr.—Marked depression on left, especially occipital	Mother has a harelip
5	5 mo.	Generalized seizures until last seen in 1953	7 3/12 yr.—Poorly organized depression in right occipital area	Negative
6	2 mo.	Left seizure, then generalized seizures until last seen in July, 1955	3 4/12 yr.—Marked depression, right parietal and occipital areas. No normal alpha waves	Negative
7	2 mo.	Right-sided seizures, then generalized or both until last seen in April, 1958	1 yr.—Marked depression, left slow wave focus in left occipitotemporal region 4 2/12 yr.—Same, plus sharp fused activity on right	Patient's identical twin is normal
8	3 mo.	Tonic seizure, then right-sided and generalized seizures	13 mo.—Slightly depressed left slow wave focus in left temporal region	Negative
9	6 3/12 yr.	No seizures; right hemiparesis at 6 3/12 yr.	6 7/12 yr.—Depression left, slow wave focus left fronto-temporal	Negative

the left eye. He also had coloboma in the same eye (Fig. 1). Two patients developed glaucoma at 3 months and 10 years of age, respectively. Except for the patient in Case 9, who was born with bilateral buphthalmos, all the patients had left-sided ocular involvement.

Involvement of the optic radiation and visual cortex by the cerebral nevus may give rise to hemianoptic defects.[24] This was observed in 2 of our patients. The actual incidence may be higher since some of our patients were too defective mentally to permit an accurate examination of the visual fields.

Other Coincidental Features.—The presence of hemangioma of the kidneys and other viscera in Sturge-Weber syndrome has been reported.[15] One of our patients (Case 4) had hematuria at 4 years of age, but no abnormality was demonstrated by intravenous pyelogram. One patient (Case 9) suffered from severe bouts of hematemesis and melena, but a gastrointestinal series showed no abnormal finding. One (Case 7) had coaretation of the aorta.

Family History.—There is no incidence of similar disease among the family members. A maternal aunt and uncle of the patient in Case 2 had hemangiomas of the arm. The mother of the same patient had hemangioma of the occipital region. The mother of the patient in Case 1 had unequal pupils and heterochromia iridis.

LABORATORY DATA

Electroencephalography.—The characteristic electroencephalographic finding in Sturge-Weber disease is a unilateral depression of cortical activity, with or without spike discharges in the affected area.[25] In cases with bilateral facial nevi and possibly bilateral cerebral lesions, the more severely affected side shows the more marked depression of activity. In early infancy the electroencephalogram may not be abnormal. This was so in Cases 4 and 8 (Table III). The depression of activity generally develops first and is followed later by the appearance of focal slow or spike activity.

Fig. 1.—Bilateral facial nevi; buphthalmos and coloboma of left eye.

TABLE III. CEREBRAL FUNCTION AND SITE OF CEREBRAL NEVUS

CASE	PRESENT AGE	MENTALITY	SPEECH	BEHAVIOR	SITE OF FACIAL NEVI IN RELATION TO TRIGEMINAL BRANCHES	INTRACRANIAL CALCIFICATION
1	11½ yr.	Normal	Normal	Normal	Right, 2nd branch	0
2	9⁸⁄₁₂ yr.	Unaware of surroundings	None	Quiet, rocks	Right, 1st and 2nd	+
3	7 yr.	Unaware of surroundings	Few words	Hyperactive	Left, 1st	+
4	12 yr.	Retardation	Fair	Hyperactive (mild)	Left, all branches Right, 1st and 2nd	+
5	13 yr.	Deficiency	Fair	Hyperactive	Right, 1st and 2nd Left, cheek-spots	0
6	7⁷⁄₁₂ yr.	Unaware of surroundings	None	Very hyperactive	Left, all branches Right, all branches	+ +
7	4½ yr.	Deficiency	2 to 3 sentences	Hyperactive	Left, all branches	+
8	15 mo.	Retardation	Just begun	Normal	Left, 1st	+
9	7 yr.	Normal	Normal	Normal	Both left and right scattered	0

Roentgenograms of the Skull.—The characteristic "tram-line" calcification is pathognomonic of this disease. Evidence of cerebral hemiatrophy with smallness of the skull ipsilateral to the nevus may be present as well. However, these radiographic findings may not be demonstrable in infancy. About one half of our patients presented typical roentgenographic findings of intracerebral calcification when first seen (Cases 2, 4, 6, and 8); the youngest patient, in whom the calcification was quite characteristic in appearance, although minimal in amount, was 13 months of age (Case 8). Two patients developed calcification under observation as they grew older (Cases 3 and 7). One patient (Case 4) showed the typical calcification at 5 years of age, with increased deposits at 10 years. Fig. 2 shows a roentgenogram of a patient with bilateral calcification (Case 6).

Pneumoencephalography.—Pneumoencephalography was carried out in 3 of our patients. Cerebral hemiatrophy with unilateral ventricular dilatation and widening of the subarachnoid sulci on the affected side was present in all 3.

Arteriography.—Although abnormal "staining" of the diseased area due to delayed emptying of the angiomatous lesions has been reported,[26, 27] no abnormal findings were demonstrated in 3 of our patients. This is in agreement with the experience of King and Schwarz.[28]

DIAGNOSIS

When classical symptoms and signs are present, the diagnosis of Sturge-Weber disease should offer no difficulty. With atypical or incomplete forms, however, the recognition may not always be easy.

Of the 144 cases reviewed by Lund,[23] 7 patients had typical radiographic findings but did not have a facial nevus. Two of these patients were Lund's

own cases and the diagnosis was proved at operation. One of Lichtenstein's patients[17] also had no facial lesion but had characteristic roentgenographic findings of the skull.

In a few cases the facial nevus does not exactly coincide with the sensory distribution of the trigeminal nerve.[28, 29] Case 9 of this series falls into this group.

scalp. Orzechowski and Novicki[32] reported postmortem findings of a patient in whom tuberous sclerosis and neurofibromatosis coexisted. In this connection one of our patients is of great interest. The father has the peripheral nodular type of neurofibromatosis. The patient has developed the classical triad of tuberous sclerosis while under observation.

Fig. 2.—Roentgenogram of skull showing characteristic calcification.

INTERRELATIONSHIP AMONG NEUROCUTANEOUS SYNDROMES

There are a number of reports in the literature attesting to a close relationship between the 3 neurocutaneous syndromes: Sturge-Weber syndrome, tuberous sclerosis, and neurofibromatosis. Greig[30] reported on a patient with typical tuberous sclerosis who had right hemiplegia. Operation disclosed an angioma of the Rolandic area. Good and Garb[31] reported a case of tuberous sclerosis with neurofibromatosis of

The patient's 2½-year-old brother has half a dozen café au lait spots over the trunk and a small cavernous hemangioma on the shoulder.

TRANSITIONAL OR HYBRID FORMS

Bizarre associations of certain features of the neurocutaneous syndromes may produce "hybrid" or "transitional" forms. These are of unusual interest from both the clinical and the pathologic viewpoints. In this respect the following case merits presentation.

CASE REPORTS

A Latin-American boy, 6½ years of age, was born with vascular nevi on both sides of the face and trunk. The eyes were very prominent and the sclerae bluish. Bouts of melena occurred at 3 years and again at 4 years of age. About 2 weeks prior to admission to the Texas Children's Hospital, he had recurrence of hematemesis and melena accompanied by marked weakness of the right side of the body. Physical and mental development were considered within normal limits. His father had telangiectatic lesions on the back; the family history was otherwise noncontributory. Examination showed bilateral and extensive port-wine nevi over the face, scalp, ears, and sclerae. The facial lesion was more extensive on the left side. The distribution on either side did not coincide with the sensory distribution of the trigeminal nerve. Both eyes were proptotic and showed glaucomatous changes on funduscopic examination. The left side of the cranium was depressed. The right limbs were weak and flaccid. The tendon reflexes were hyperactive on the right and moderately active on the left. There was sustained ankle clonus on the right and unsustained clonus on the left. The plantar responses were extensor bilaterally. The roentgenogram of the skull showed no intracranial calcification. Carotid arteriography showed bilateral arteriovenous angiomas with suggestive evidence of a hematoma in the left occipital region.

Comments.—This case presents several unusual features: (1) The distribution of the facial nevus did not follow that of the sensory branches of the trigeminal nerve. (2) The angiomatous malformation in Sturge-Weber disease is usually telangiectatic but may be arteriovenous or venous.[33] In this patient there was arteriographic evidence of cerebral arteriovenous angioma. (3) The extensiveness of the cutaneous lesions, the repeated episodes of gastrointestinal hemorrhage, and the fact that the father had telangiectatic lesions on the back suggest that the vascular anomaly may be widespread. One of the cases reported by King and Schwarz[28] is similar to this one. Lichtenstein pointed out that there are a variety of hemangiomatous states and not all of them lead to calcification of the cerebral cortex. Osler's disease (hereditary hemorrhagic telangiectasia) may involve skin, meninges, and brain in addition to viscera.[17] Although we consider this case as a "variant" of Sturge-Weber disease, the possibility of its being a transitional hybrid form between Sturge-Weber and Osler's disease remains an attractive speculation.

Another case deserves mention at this point.

A 19-month-old Negro child had been seen for left-sided focal seizures since 17 months of age. Past history was negative except for a "birthmark" on the face. Examination showed a pigmented area (café au lait) over the distribution of the first two branches of the right trigeminal nerve. The electroencephalogram at 17 months of age showed continuous seizure discharges arising from the right occipitotemporal region. A repeat EEG at 20 months showed diminished voltage in the same region with sharp and slow wave activity. Further investigations could not be carried out because of lack of cooperation.

This case does not fit into any recognized category, but it emphasizes the association of skin changes in the trigeminal distribution with ipsilateral occipital epileptogenic lesions and again raises the question of a developmental anomaly affecting both regions.

Recently Boder and Sedgwick[34, 35] reported 8 cases of a syndrome characterized by progressive cerebellar ataxia with onset in infancy, striking telangiectasia of the bulbar conjuntivae and other facial areas, susceptibility to pulmonary infections, and a tendency to familial occurrence. They proposed the term "ataxia-telangiectasia" and suggested that it be considered as the fifth form of phakomatosis. None of our cases appeared to be of this type.

TREATMENT

Medical therapy in Sturge-Weber disease is seldom very satisfactory. Anticonvulsant medication may alleviate the milder cases but often fails when the seizures are very numerous and severe. Furthermore, the neurologic deficits tend to progress with age so that the effectiveness of medical treatment may decrease with progression of the disease. Radiation therapy including roentgen ray and radium has proved to be of no value.[36]

A number of surgical procedures have been developed since Cushing's first attempt in 1906.[5] Even though he merely separated the adhesions between the meninges and the cortex in his second case, this procedure was reported to have resulted in cessation of seizures. Excision of the diseased portion of the brain has been carried out by a number of surgeons.[37, 38] Recently, hemispherectomy has been advocated for selected cases with unilateral lesions. The reported results are encouraging.[39, 40] This radical surgical approach should be reserved for those patients in whom anticonvulsant therapy has failed and in whom the deficit following operation would not be worse than the preoperative status. In Case 2 a hemispherectomy[41] was done. Following operation, the seizures which had been incapacitating stopped. In Case 3 a block resection of the cerebral lesion was performed (by Dr. James Greenwood, Jr.). This also was followed by complete cessation of seizures. The patient's behavior was improved, and his mentality and speech showed slight but definite improvement. Physically, a very remarkable growth spurt occurred postoperatively.

The surgical specimen was examined by Dr. E. C. Alvord, Jr. The following is his report:

"Gross: The resected brain consisted of the occipital, parietal and posterior temporal lobes from the left hemisphere. There is diffuse subarachnoid hemorrhage over the lateral aspect. The calcarine fissure is identified and is seen not to extend to the occipital pole. The parietooccipital fissure is identified externally also. An x-ray of this specimen reveals linear calcifications in the occipital pole extending approximately 3 cm. anteriorly from the pole. On cut surface the stria of Gennari is very poorly represented. No gritty sensation it felt on cutting, but there are pale yellow granular zones within the middle regions of the gray matter.

"A second piece of brain is much smaller than the first and appears to be anterior temporal lobe. On cut section ventricle and hippocampus are identified and appear normal.

"Microscopic: H & E, trichrome, Nissl, myelin, iron, and Von Kossa preparations of the occipital, temporal, and parietal lobes reveal increased vascularity of the leptomeninges and calcification of the brain. These are most marked in the occipital lobe, as noted by x-ray, but small foci are present in the other regions (specifically in the superior and inferior parietal lobules at the level of the tail of the

caudate nucleus, in the superior temporal gyrus and in the caudal temporo-insular junction). The meningeal vessels are thin-walled, closely packed venules, and are not calcified. They do not generally extend into the cortex; but in two places there is marked gliosis and irregular scalloping of the adjacent cortex, and here there is slight penetration of vessels but only into the molecular layer.

"The cerebral calcification is present in the middle regions of the cortex (layers 3 and 2) but in places diffuses into the deeper regions and also into the white matter. The deposits are usually round, rarely elongated or irregularly lobulated, the larger ones crystalline, the smaller ones surrounded by a thin non-calcified capsule. The calcifications occur on all surfaces of the occipital lobe, especially on adjacent sides of sulci near the crests of gyri. There is extensive degeneration and distortion of the occipital lobe: the calcarine fissure is very shallow, and there is a microgyria of the supra-calcarine gyri where the degeneration is most marked. In myelin stains there is a relative loss of U-fibers with less degeneration of deeper white matter; this is particularly evident in the temporal lobe, where the other lesions are least marked [Fig. 3].

"Impression: These changes are characteristic of Sturge-Weber's disease with leptomeningeal telangiectasia and intra-cortical calcification. It is doubted that the calcification is of blood vessels; it is more likely that the calcium is deposited in areas of pseudo-laminar cortical necrosis secondary to ischemia caused by the leptomeningeal vascular anomaly, but why the calcification occurs in this disease and not in other cases with pseudo-laminar necrosis is not apparent. The degeneration of U-fibers is difficult to explain, since it also occurs in the temporal lobe where the cortex is practically intact."

Fig. 3.—Low-power photograph of section of left occipital cortex stained by Nissl's and von Kossa's techniques. Note leptomeningeal telangiectasia, loss of neurones, and calcification most prominent in middle layers of cortex.

Photographs of this patient and the gross appearance of the lesions at operation were previously published.[42]

IMPORTANCE OF EARLY SURGICAL INTERVENTION IN SELECTED CASES

In view of the natural history of the disease it would appear that unilateral

lesions suitable for surgical removal should profit more from the procedure the earlier it is carried out. This question was considered when the patient in Case 8 was first seen. The infant had right-sided paresis and seizures but otherwise was in good condition. Intracerebral calcification was present and the electroencephalogram showed depressed activity on the left side. It was our opinion that surgical intervention at this time might prevent the development of mental, speech, and behavioral disorders in addition to providing immediate symptomatic relief of the seizures. The later the operation is carried out, the greater is apt to be the functional deficit which cannot be restored.

Two of the 4 patients with glaucoma required operation for the relief of intraocular tension. One patient responded to Diamox therapy, which in this case served as an anticonvulsant as well as an antiglaucomatous agent.

PROGNOSIS

The prognosis is dependent upon the extent of the cerebral lesion, the rapidity of its progression, and the response to medical or surgical treatment. The control of seizures is important but is not the sole determinant of the prognosis. The total functional potentialities of the patient in terms of mental capacity, behavioral adaptation, and speech and visuomotor coordination are important factors which may become progressively impaired.

DISCUSSION

The Sturge-Weber syndrome, tuberous sclerosis, and neurofibromatosis exhibit remarkable parallelism in their clinical and pathologic manifestations. All three are the result of congenital ectodermal and mesodermal maldevelopment differing only in the period of embryonogenesis during which the development of the structural defect takes place.[20] The predominance of one or another of the ectodermal structures affected and the degrees of participation of mesodermal elements further differentiate the ultimate clinical picture into one of the three entities of the neurocutaneous syndromes.

The three conditions may overlap with a wide range of variability owing to the interplay of factors permitting many combinations of developmental defects. It seems clear that tuberous sclerosis and neurofibromatosis are more closely related to each other than to Sturge-Weber disease. In both tuberous sclerosis and neurofibromatosis, ectodermal anomalies, such as pigmentary and depigmentary changes, fibromatous growths, and retinal tumors predominate over mesodermal anomalies. Definite familial or hereditary tendencies may be present in both conditions. On the other hand, in Sturge-Weber disease, mesodermal hyperplasia overshadows ectodermal malformations. Pathologically as well as clinically, it differs from the other two.

SUMMARY

1. Sturge-Weber disease is a congenital vascular malformation of the skin and leptomeninges.

2. The facial nevi usually follow the trigeminal nerve distribution. Skin nevi may in addition involve other areas roughly following dermatomal demarcation.

3. The lesions in the brain are most likely secondary to the angiomatous malformation of the overlaying leptomeninges. Characteristic calcifications are formed in the cerebral cortex, as well as in the angioma.

4. Eight typical cases of Sturge-Weber disease are summarized.

5. The earliest calcification appeared in roentgenogram of the skull of a patient 13 months of age.

6. One unusual "hybrid transitional" case is also presented.

7. The suggestion is made that early surgical extirpation of unilateral lesion may prevent functional deterioration as well as bring symptomatic relief from seizures.

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ACUTE PANCREATITIS ASSOCIATED WITH CONGENITAL CYST OF THE COMMON BILE DUCT

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PANCREATITIS in association with disease of the biliary tract is an established clinical syndrome, but acute pancreatitis in childhood subsequently relieved by internal drainage of an obstructing congenital cyst of the common bile duct is a rarely reported entity which may present difficult diagnostic and therapeutic problems. Such a case was seen recently in the Harriet Lane Home and is presented because if its unusual features. The combination[1] has received such little previous attention that further discussion does not seem superfluous.

CASE REPORT

H. L. H. B-38096.—This 3-year-11-month-old Negro girl was admitted to the Harriet Lane Home on Sept. 3, 1958, with vomiting and abdominal pain of 7 days' duration. Except for one episode of pneumonia, her past general health had been good, without history of previous abdominal pain, vomiting, or jaundice.

Six days prior to admission the patient complained of abdominal pain and subsequently vomited everything taken by mouth. The next day (Aug. 29, 1958) she was examined as an outpatient and no abnormalities were noted. She was treated for nonspecific gastroenteritis and followed daily until admission. During this period the vomiting subsided but the abdominal pain persisted. Three days before admission she was noted to have tenderness in the right upper quadrant. The patient remained afebrile throughout the outpatient course. The laboratory studies during this period were: Ausust 30: urine, negative except for 1 plus coproporphyrin; blood lead, 0.021 mg. per cent (normal range, 0.01 – 0.04 mg. per cent). September 2: white blood cells 8,600; normal differential; hematocrit, 37 per cent; sickle cell preparation, negative; chest x-ray, normal; bilirubin, 2.1 mg. per cent total and 1.1 mg. per cent direct; cephalin flocculation, 0; thymol turbidity, 1.3 units; serum amylase, 1,105 Somogyi units.

The patient was admitted with a presumptive diagnosis of acute pancreatitis. The vital signs were: temperature, 37.2° C.; pulse, 88; respirations, 24, and blood pressure, 85/60. She was in the tenth percentile for both height and weight. The skin turgor was poor and the mucous membranes dry. There was marked tenderness and muscle guarding in the right upper quadrant; palpation in this region was unsatisfactory. Some observers, however, felt a small mass along the upper lateral border of the right rectus muscle. The bowel sounds were normal as was the remainder of the physical examination.

Laboratory studies on admission (September 3) revealed: urine, acetone 4 plus, sugar, protein, and microscopic,

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negative; white blood cells, 8,000; CO_2 (combining power), 24.6 mEq. per liter; chlorides, 92.3 mEq. per liter.

X-ray of the abdomen showed well-outlined renal and psoas shadows and no splenic or hepatic enlargement. The upright film showed a horseshoe-shaped portion of the small bowel in the mid-abdomen suggesting the "sentinel loop" sometimes seen in pancreatitis.[2]

Hospital Course.—She was maintained on intravenous fluids, gastric suction, atropine, penicillin, and streptomycin. The following laboratory tests were obtained: September 4: CO_2 (combining power), 30.0 mEq. per liter; chloride, 90.0 mEq. per liter; Na, 145.0 mEq. per liter; K, 5.3 mEq. per liter; Ca, 11.4 per cent; total protein, 7.7 mg. per cent; albumin, 6.0 mg. per cent; amylase, 684 somogyi units; cephalen flocculation, 0; thymol turbidity, 1.0 units; bilirubin, total, 7.6 mg. per cent, direct, 5.0 mg. per cent; glucose, 114 mg. per cent.

On the third day of hospitalization the temperature rose to 38° C., bowel sounds were diminished, and the patient became noticeably icteric. Because of failure to respond to nonoperative therapy, and because of increasing evidence of acute cholecystitis, an exploratory laparotomy was performed.

A transverse right upper abdominal incision was made. The palpable mass was a large, tense, otherwise normal gall bladder without stones. There were numerous fibrinous adhesions about the porta hepatis, but no evidence of bile peritonitis. The panereas was edematous and indurated but there was no fat necrosis or cyst formation. At the junction of the common duct with the duodenum a large tense cystic mass was present which measured 2½ inches in diameter. Clear sterile bile was obtained on needle aspiration. The duodenum was then mobilized medially and a short duodenotomy performed. There was no bile in the duodenum. A probe was passed through the normal ampulla and no stone or mass encountered; a very small amount of bile escaped from the duct when the probe was withdrawn. A transverse incision was then made in the tense cyst above the superior border of the duodenum and 40 c.c. of dark clear bile removed. Following this decompression, normal bile flowed spontaneously into the duodenum. An attempt to identify the communication between the cyst and the common duct met with failure.

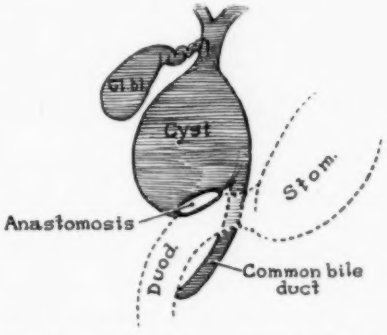

Fig. 1.—Choledochoduodenostomy used for drainage of congenital cystic dilatation of common duct.

The proximal dilated common duct was easily entered with a probe through the ampulla and lay behind the cyst. A cyst duodenostomy was then performed between the cyst opening and the duodenum which lay adjacent and parallel to each other. This was elected as a more rapid means of internal drainage than a Roux-Y jejunal loop. Drains were placed to the anastomosis and the wound closed with fine silk.

The patient's postoperative course was uneventful. On the fifth postoperative day (September 9) the laboratory results were: bilirubin, total, 1.6 mg. per cent, direct, 0.4 mg. per cent; amylase, 360 Somogyi units.

The patient was discharged on the tenth postoperative day. She has been followed in the outpatient department since that time and has remained well in the ensuing 8 months.

DISCUSSION

Pancreatitis unassociated with mumps is a rare disease in childhood. Blumenstock,[3] was able to find only 31 cases in reviewing the literature, to which he added 4 of his own. The symptoms in childhood are not unlike those seen in adults and include abdominal pain and tenderness, vomiting, tachycardia, and a slight fever. The diagnosis may be suspected on these clinical findings, but must be confirmed by an elevated serum amylase. Commonly, the serum bilirubin is slightly elevated, but clinical jaundice is extremely rare.

Initially, this patient was thought to have acute pancreatitis (the serum amylase of 1,105 Somogyi units was considered diagnostic). Elevations of the serum amylase can, of course, occur with secondary inflammation of the pancreas from peritonitis or penetrating ulcers or from more remote causes such as high intestinal obstruction or impaired renal function. In studying conditions other than pancreatitis associated with an elevated amylase, Raffensperger[4] noted maximal values of 388 Somogyi units with diaphragmatic hernia, 326 Somogyi units with intestinal obstruction, and 326 Somogyi units with impaired renal function. The indication for operative intervention was the rising direct serum bilirubin and the questionable abdominal mass. The pancreatitis was not considered a contraindication to exploration. The high mortality associated with operations for pancreatitis is probably due to unnecessary and traumatic dissection in the region of the pancreas rather than to the often mandatory diagnostic laparotomy itself.[5]

In an attempt to clarify the relationship between pancreatitis and congenital cystic dilatation of the common bile duct, a review of the literature concerning choledochal cysts was undertaken. Approximately 265 cases have been reported through 1957. In 1956 Tsardakas[6] was able to summarize 242 cases subsequent to which we have found 23 cases not included in his paper.[1, 6, 8-17] A number of excellent review articles[6, 7, 18-21] have been written, and the symptomology, treatment, and probable pathogenesis have been greatly clarified. The triad of pain, jaundice, and palpable tumor, especially in a young girl, is now strong presumptive evidence for cystic dilatation of the common duct. This triad is not constant, however, since in Tsardakas'[6] review, pain occurred in 63.3 per cent, jaundice in 69 per cent, and tumor in 72 per cent. The pain is usually intermittent, is localized to the right upper quadrant, and is often associated with nausea and vomiting. The jaundice may also be intermittent and is sometimes associated with alcoholic stools.

The cysts vary in volume from 30 to 5,800 c.c. and usually involve the common duct alone. The fact that the cystic area is localized and eccentric serves to distinguish it from the more generalized dilatation of the biliary system which may follow purely obstructive lesions. The cysts are thought to be congenital in origin.

All authors agree that the only definitive treatment is surgical. Various operations have been employed. External drainage has been unsatisfactory and excision of the cyst has been accompanied by a very high mortality. Direct anastomosis of the cyst to the

duodenum or through a Roux-Y loop to the jejunum have become the operations of choice.

These reviews, do not, however, mention a possible association with pancreatitis. Zinninger,[21] in fact, eliminates such cases, saying, "No account has been taken of cylindric enlargements such as not infrequently occur after partial or complete occlusion of the common duct by stone, tumor, traumatic stricture or pancreatitis. In a few such cases there has been cystic dilatation. . . ." He gave references to such cases, one of which (Fowler's[22]) seemed to fit the criteria for cystic dilatation of the common duct. In this case "the cystic duct was enlarged and tortuous. The common duct was dilated to the size of an orange and had the appearance of a cyst. Evidence of chronic pancreatitis was present (areas of old fat necrosis)." Gross,[18] Poate,[19] and Shallow[7] do not mention associated pancreatitis. Tsardakas[6] also makes no general statement about pancreatitis, although 2 of his 3 patients had elevations of the serum amylase, one having had a previous operation for suppurative pancreatitis. Ravitch[1] does mention that pancreatitis can occur with choledochal cysts and cites one patient of Grove's, who had an elevated amylase, as well as Tsardakas' 2 patients. One of Dr. Ravitch's patients had an elevated serum amylase after operation, but since her bile and pancreatic ducts had been injected with a radiopaque material for operative cholangiography, the significance of this finding is questionable.

Review articles on pancreatitis[23] were of little help in elucidating a possible relationship between the 2 disorders. Blumenstock's[3] review of 35 cases in children does not suggest any association. Paxton[24] reviewed 307 proved cases of pancreatitis from all age groups and even though he found 125 with biliary tract disease, cystic dilitation of the common duct was not mentioned.

Since the general reviews gave little indication concerning the presence or absence of associated pancreatitis, specific case reports of cystic dilatation of the common bile duct were examined. A total of 87 case reports were found.[1, 6-17, 19-22, 25-70] Twenty-five of the 87 patients had postmortem examinations.[20, 21, 25, 28, 31-34, 36, 38, 39, 42, 43, 45, 47, 49, 51, 52, 55, 58, 61, 69]

Two of the autopsied patients[39, 47] had peripancreatitis which was presumably secondary to peritonitis. One had pancreatitis believed to be secondary to serosal metastasis from a liver carcinoma. In only one case[43] was the pancreatitis thought to be associated with a congenital abnormality. This case (Table I, Case 2) was unusual in that there were 2 pancreatic ducts opening into the choledocal cyst and both of these pancreatic ducts were also cystic. The other 22 autopsy reports either failed to mention the pancreas or stated that it was normal. None of the patients who died had amylase determinations.

Of the 60 patients that recovered only 7 had any chemical test made of pancreatic disease. Two patients[54, 62] were found to have normal serum amylase values and one[17] had a normal urinary diastase of 12 units. Ravitch's patient did have an elevated serum amylase, but this may well have been iatrogenic. The pertinent findings, in the other 3 cases[6, 8] in which the

TABLE I. CASES OF CYSTIC DILATATION OF THE COMMON BILE DUCT COMPLICATED BY PANCREATITIS

AUTHOR	AGE	SEX	JAUNDICE	MASS	PAIN	FEVER	WBC	AMYLASE	REMARKS
Fowler[22]	22	M	Yes	No	Yes	—	—	—	Cystic dilatation of common duct (size of an orange); areas of old fat necrosis thought to indicate chronic pancreatitis; cyst drained externally; patient died, autopsy refused
McWhorter[43]	49	F	Yes	Yes	Yes	—	—	—	Hepaticoduodenostomy with relief of symptoms; pancreas firm and sclerotic. 7½ years postoperatively developed diabetes; died age 63; autopsy showed dilatation of bile and pancreatic ducts and extensive pancreatitis.
Tsardakas[6] (Case 1)	34	F	No	No	Yes	No	—	2,600	At age 33 had operation for suppurative pancreatitis at another hospital; sphincterotomy was followed by recurrence of symptoms and also jaundice; a cystoduodenostmy alleviated all symptoms
Tsardakas[6] (Case 3)	58	M	Yes	Yes	Yes	Yes	9,600	1,281	Cholecystectomy and cystoduodenostomy; all symptoms relieved.
Grove[8]	9	F	Yes	Yes	Yes	Yes	—	500	Cured by Roux-Y cystojejunostomy
Present case	3	F	Yes	Yes	Yes	Yes	8,000	1,105	Pancreas indurated, sclerotic and edematous; cystoduodenostomy alleviated all symptoms

serum amylase determinations seemed to indicate pancreatitis are listed in Table I.

Including the case reported here, the case of Fowler's, the 3 cases with elevated serum amylase values, and the case with the cystic pancreatic ducts, there are 6 cases of cystic dilatation of the common bile duct which had an associated pancreatitis. Dr. Ravitch's case may be the seventh. The autopsy findings do not suggest that severe pancreatitis is a frequent complication, and the fact that the patients who have recovered after operation do not show signs of pancreatic insufficiency indicates that extensive pancreatitis is an infrequent associated condition. The high serum amylase values in the few cases in which it was determined may reflect the fact that the clinician's suspicion was aroused only in the obviously symptomatic instances. Since, however, a choledochus cyst alone can cause acute abdominal pain and tenderness, it is difficult to understand how the uncomplicated case differs greatly from one that has both a choledochus cyst and pancreatitis.

It seems clear that pancreatitis is sometimes, though perhaps rarely, associated with cystic dilatation of the common bile duct. The causal relationship is not clear in every case but is probably explainable on the basis of obstruction of the pancreatic duct by the large tense cyst or by reflux into the pancreatic duct. More frequent determinations of serum amylase in these patients may help determine the actual frequency of association between pancreatitis and congenital cystic dilatation of the bile duct.

SUMMARY

A case of congenital cystic dilatation of the common bile duct with an associated pancreatitis is presented. The literature is reviewed in an attempt to find the frequency of such an association. Five other cases were found in which both conditions coexisted.

The symptoms of pancreatitis are not always sufficiently different from those of choledochus cyst to ensure the simultaneous diagnosis of both diseases when they occur together. Therefore, an awareness of the possible association may be helpful.

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Erratum

In the article entitled "A Disturbance of Carbohydrate Metabolism Caused by Lesions of the Central Nervous System" by R. D. Brooke Williams, M.D., which appeared in the March, 1959, issue of the JOURNAL, page 299, the blood sugar level taken on admission to the first hospital was omitted. It was 212 mg. per cent.

Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, *Editor*
John M. Craig, *Assistant Editor*

THE patient in this case was a girl who at the time of her terminal illness was 9 9/12 years of age. At the age of 5½ years she developed a poor appetite and listlessness. Four months after the onset of her illness, she began to have abdominal pain. Except for an injury to the left eye with a resulting hemorrhage and glaucoma, the past and family histories were not remarkable.

At the time of admission, at age 5½ years, she was pale and thin, with an irregularly round, dilated left pupil, which did not respond to stimulation with light. The heart was not enlarged, but a rough, high-pitched systolic murmur was heard all over the precordium. The liver was palpable 5 cm., and the spleen 7 cm., below the costal margin, the latter occupying the entire left flank. The superficial lymph nodes were all uniformly enlarged.

The initial hemogram gave the following values: hemoglobin 5.9 Gm. per cent; and erythrocytes 2.09 million per cubic millimeter; leukocytes, 500,000, and platelets, 656,000 per cubic millimeter. The differential leukocyte count was: blasts 1 per cent; polymorphonuclears, 20; promyelocytes, 3; eosinophils, 1; myelocytes, 7; metamyelocytes, 26; band forms, 33; eosinophilic metamyelocytes, 3; basophils, 4; and lymphocytes, 2. The reticulocytes were 2 per cent of the total erythrocyte count. A bone marrow aspiration revealed a hyperplastic marrow with a differential count of: blasts, 1 per cent; mature granulocytes, 40; immature granulocytes, 53; lymphocytes, 3, and erythroid elements, 3. Roentgen studies disclosed a failure of tubulation of the distal femoral shafts.

Treatment with Amino-an-fol and Teropterin resulted in a fall in peripheral leukocyte levels, but no significant clinical improvement. The patient was discharged 6 days after admission, showing little improvement. She was readmitted for transfusions 2 months later. Over the next 6 months there was little evidence of change in her peripheral blood status, transfusions being required to maintain the hemoglobin levels. Seven months after her first admission the peripheral leukocyte count rose to 1 million, and 8-Azoguanine was started. This had no significant effect upon her laboratory or clinical status.

Seven and one half months after her original entry, she was readmitted for x-ray therapy. At this time, papilledema and a greatly enlarged spleen were noted on physical examination. Three hundred roentgens was delivered to the spleen over a 2 week period. One month later the spleen had decreased markedly in size, the peripheral leukocyte count had fallen to a range of 20 to 30 thousand, and her general sense of well-being had improved.

Ten months after her original admission, at age 6 3/12 years, the peripheral leukocytes again began to increase. For this reason a splenectomy was scheduled. Before splenectomy, the liver was palpable 2 cm. below the costal margin, and the spleen 9 cm. below. The circulating leukocytes numbered 38 thousand and the platelets 298 thousand. After splenectomy the leukocyte level fell to 34 thousand, but the platelets rose to 1 million per cubic millimeter. Four weeks after operation, the leukocytes had risen to 150 thousand, but the platelets had fallen to 400 thousand. The child continued to do well.

At the age of 6 9/12 years, urethane was given; over a 5 week period the leukocyte count was reduced to 20,000 per cubic millimeter. For the next 8 months urethane medication was continued with fair control of the peripheral counts, until increasing doses caused gastrointestinal toxicity which necessitated its discontinuance.

Twenty-five months after her original admission, at age 7½ years, triethylenemelamine was given because of rising leukocyte and platelet counts. Neither this, Fowler's solution, triethylenephosphoramide, nor nitrogen mustard, given serially over the next 8 months, caused any significant change in the hematological picture, though the child continued to do fairly well clinically. At age 8 4/12 years, urethane was again given with a resultant gradual fall over the next 6 weeks to a peripheral leukocyte level of 50,000 per cubic millimeter.

Twenty days prior to her last admission, at age 9 9/12 years, the patient was thought to have been exposed to measles. Three days before admission she developed a frontal headache, a hacking cough, lethargy, and fever. These were unaffected by the administration of tetracycline.

At the time of admission, the temperature was 101.8° F., pulse, 110, and respirations, 28 per minute. There were decreased resonance and decreased breath sounds over the entire right chest. Fine râles were heard anteriorly and posteriorly on the right during both inspiration and expiration. The left side of the chest was clear and resonant.

The peripheral count was leukocytes, 191 thousand, and platelets, 3.5 million per cubic millimeter. The differential smear gave the following values: mature granulocytes, 78 per cent, immature granulocytes, 13, monocytes, 5, eosinophils, 3, and basophils 1. The hemoglobin was 6.9 Gm. per cent. The spinal fluid was negative and two blood cultures gave no growth. The chest roentgenograms showed a progressively severe bilateral infiltration. An electrocardiogram on the day of death was essentially normal.

Bilateral râles were heard on the second hospital day, and these persisted throughout both lungs until death. Respiratory distress increased and was not relieved by oxygen. Venous distention of the neck was

noted. Penicillin and streptomycin, as well as digitalis, were given without evident effect on the relentless course of the disease. She died 6 days after admission.

DR. FELIX P. HEALD.*—I think that if we inquire into the history a little more carefully we might discover symptoms of anemia referable to the hemoglobin of 6 Gm. Abdominal pain is very common in chronic myelogenous leukemia, and is not uncommon in the period prior to the establishment of the diagnosis. It is due to rapid expansion in the size of the spleen or to the development of small infarcts with perisplenitis. Either situation may be severe enough to mimic a "surgical abdomen."

The murmur heard on physical examination may have been related to the profound anemia; it was not referred to again.

The spleen was enlarged. Such enlargement tends to be much more marked in chronic myelogenous leukemia than in chronic lymphatic leukemia. The moderate enlargement of the lymph nodes also fits in with myelogenous leukemia rather than chronic lymphatic leukemia in which the lymph nodes tend to be quite large. It is of interest that the hemoglobin and red cell count were so low in this child. They need not be when such patients are first seen. Polycythemia has been described in chronic myelogenous leukemia with erythroid hyperplasia in the bone marrow. Mature segmented forms may comprise 30 to 60 per cent, and metamyelocytes 20 to 50 per cent of the cells in the peripheral smear. The striking thing about the peripheral smear and the bone marrow in chronic myelogenous leukemia is their similarity. This is especially true with this girl.

The clinical course of the disease extended over 3 years, in which the patient's status waxed and waned according to various kinds of treatment that were used in attempting to control the chronic myelogenous leukemia. Since she had several transfusions, there are several possible reasons for her anemia. One is blood loss from hemorrhage. A second is a replacement of the bone marrow by leukemic cells. A third cause is the excessive destruction of red cells. Evidence of the latter lies in finding products of excessive red cell destruction in either the urine or the stool, or hemosiderin in the tissue sections, or by demonstration of a shortened red cell survival time. We have no data to support any of these etiological possibilities, however.

Eight months after the onset of leukemia, she had papilledema which may mean central nervous system involvement. Whether such involvement is of the meninges, or invasion of the brain to give increased pressure, or perhaps involvement of the optic nerve itself, is not known. In about two thirds of the cases of chronic myelogenous leukemia in adults, direct invasion of the retina or clumps of invasive cells along the vessels are found, which represent a complication of the progression of the disease.

Six weeks after a temporary improvement, following radiation to the spleen, the patient had another relapse, and splenectomy was considered. What criteria should we use for splenectomy? It is not always on a hematological basis. It is sometimes mechanical. The huge size of the spleen itself

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may be enough of an indication. Another indication may be a demonstrated hemolytic anemia. Splenectomy obviously helped this girl since she no longer had the mechanical problem of carrying a big spleen in her abdomen.

The child was admitted for the last time more than 3 years after the initial diagnosis was made with a history of headache over the frontal area and fever for 3 days. I would like to ask about the probability of exposure to measles and whether gamma globulin was given.

DR. RUDOLPH TOCH.—The child rode in a Red Cross car with another child who subsequently developed measles but it is not known whether she was in the prodromal stage. There is no indication in the record that she was given gamma globulin. She was getting blood transfusions off and on and I presume that she got some gamma globulin that way.

DR. HEALD.—What drug was she on at that time?

DR. TOCH.—She was on urethane at that time.

DR. HEALD.—Did the child cough up blood at all during the terminal illness?

DR. TOCH.—No, she did not.

DR. HEALD.—I wonder if we could see the x-rays?

DR. MARTIN H. WITTENBORG.—The initial film showed a very slight degree of undertubulation of the distal femoral shaft, which is a fairly nonspecific change. The liver was very slightly enlarged, and the spleen very much enlarged; later the spleen enlarged to the pelvic brim, but there was very little enlargement of the liver. One of the later films showed a compression fracture of one of the lumbar vertebrae.

We have three chest films made on the last admission. On the first one there are tiny densities scattered throughout the lungs with more on the right than on the left, which do not conform to a normal vascular pattern (Fig. 1). These suggest a miliary type of infiltrate. On the next film, the densities are slightly more prominent. The last film shows a very dramatic change, the lungs being heavily peppered with infiltrates and the air-containing bronchi standing out by contrast.

This represents a massive displacement of air in the lung by something fairly radiodense. This could be one of several things, such as massive aspiration, a bronchopneumonic process, a mild interstitial inflammatory process, a diffuse infiltration of a non-inflammatory type secondary to a lipoid pneumonia or granuloma, massive bleeding, or a leukemic infiltration, though I have seen very few leukemic infiltrations in the lungs.

The history here is important. These little densities appeared quickly, and they gradually became confluent, until there was a replacement of the normal air-containing spaces of the lung after 12 days of illness, which would in itself eliminate a number of entities from our consideration.

DR. HEALD.—Would a leukemic infiltrate develop that rapidly?

DR. WITTENBORG.—There is a great disparity of opinion about that. We feel we cannot distinguish leukemic infiltration from peribronchial inflammatory infiltration. Regardless of

whether the white cells migrate in response to bacteria or viruses or come out as a result of leukemia, the distribution pattern is the same. We have few criteria for distinguishing between the two. The last one I saw I considered to be an inflammatory infiltrate although I believe it turned out to be leukemia at postmortem. The only differentiatial point is that, if the infiltrate is not diffuse, we assume it to be inflammatory.

DR. HEALD.—Is there any evidence of pleural involvement on the last film?

DR. WITTENBORG.—There is not.

In leukemia hemorrhage occurs when when there is severe thrombocytopenia; in this case we have the opposite. There were 3½ million platelets per cubic millimeter. Theoretically, there are two possibilities for this increase in platelets. The first is that the thrombocytes, which are effective in curtailing hemorrhage, are actually increased —the paradoxical situation of a high level of circulating platelets and hemorrhage, with normal bleeding and clotting times.[1] The other unusual complication of a high circulating platelet level is thromboembolism.

Fig. 1.

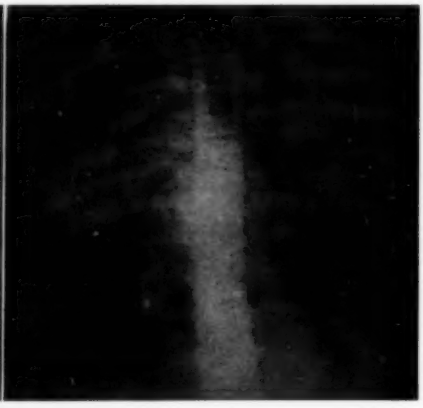

Fig. 2.

Fig. 1.—Roentgenogram of the chest at the time of final admission to the hospital.
Fig. 2.—Roentgenogram of the chest 2 days before death.

DR. NICHOLAS STAHL.—Could this represent multiple embolizations of the lung?

DR. WITTENBORG.—That would be very unlikely. It would not give an even distribution such as we have here.

DR. HEALD.—Her terminal illness, then, was characterized by fever, respiratory distress, and obvious pathologieal pulmonary findings, and a possibility of right-sided heart failure, as evidenced by venous distention.

This has been described in patients after splenectomy.

Recently, Rheinlander[2] at the New England Center Hospital reported on 410 splenectomies for various blood dyscrasias; in only 2 of these cases was there evidence of thromboembolism. Pulmonary infaretion should be considered in this case in view of the patient's roentgen changes and her high peripheral leukocyte and platelet levels, the former giving a greater

viscosity to the blood. She did not spit up blood, which is ordinarily associated with the hemorrhage or infarction, but she had right-sided heart failure, which presumably could be caused by acute pulmonary hypertension secondary to thromboembolic pulmonary obstruction.

Children with leukemia are unusually susceptible to infection and I think this girl was probably no exception. They usually have poor antibody formation in response to antigenic stimulation. This girl's spleen had been removed also, which added the hazard of overwhelming infection. The chemotherapeutic agents used may alter the immune response, as well as the disease itself. She was exposed to what was presumed to be measles 17 days before the onset of her symptoms of fever, headache, dry cough, and "pneumonia." The incubation period was in the upper range of normal. She did not have a rash, photophobia, conjunctivitis or Koplik's spots. It is theoretically possible that, in this sort of host, the immune-reactive response may be so altered that an atypical disease would occur. Pinkerton[3] apparently described such cases in infants under the term "giant cell pneumonia" in 1945. Recently a case was reported of a young infant with leukemia who developed interstitial pneumonia, subsequently died, and had giant cell pneumonia with giant cells also in the liver and pancreas.[4] This infant had very good evidence of clinical measles, unlike our present case.

Tuberculosis should be mentioned as a differential possibility but there is no history of contact.

In summary, then, this child had chronic myelogenous leukemia and died from respiratory embarrassment. Is this an atypical response to measles virus with pneumonia or is it the syndrome of thrombocytopenia with diffuse hemorrhage into the lungs? I favor the latter and would expect to find diffuse leukemic infiltrations in the kidneys, the liver, the bone marrow, and possibly the brain.

DR. CHARLES A. JANEWAY.—It is interesting that, when this child was admitted, her leukocyte differential count was that of a normal child with no abnormal cells in the peripheral blood. If there were multiple arterial thrombi in the lungs creating this picture, it must have been a very extensive process. She did not cough up blood and I doubt if the electrocardiogram would be normal in the face of this much embolic obstruction to the pulmonary blood flow. Most likely, this patient had an infection such as a widespread tuberculosis, fungus, measles, virus, or other secondary infection.

DR. HEALD.—I agree. I think she should have good evidence of electrocardiographic change. We had one example a short time ago of multiple thrombosis in the lungs of a leukemic patient who very rapidly developed right-sided failure with all evidence of right-sided obstruction.

DR. JANEWAY.—The child's platelet level is just out of my experience. It seems fantastic to me that blood can circulate with this many platelets without the formation of thrombi.

DR. CRAIG.—Dr. Toch, how often do you get this many platelets?

DR. TOCH.—We have seen them in one other child.

DR. JANEWAY.—Over a long period of time or just at the onset of their leukemic state?

Fig. 3.

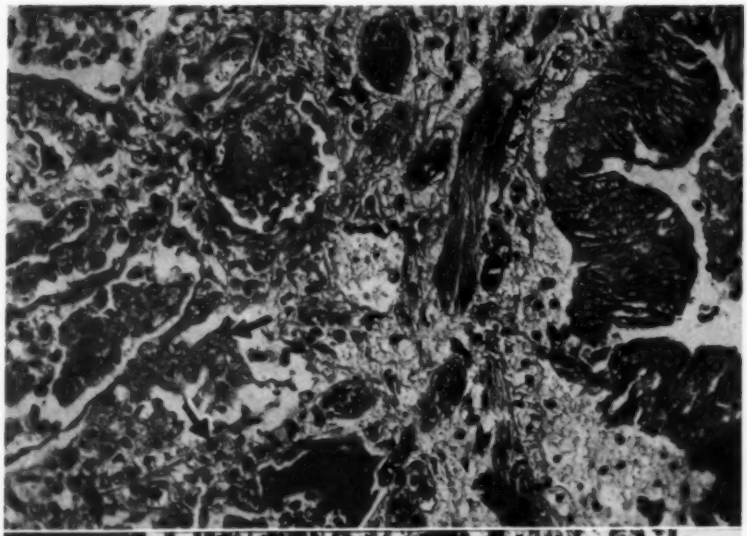

Fig. 4.

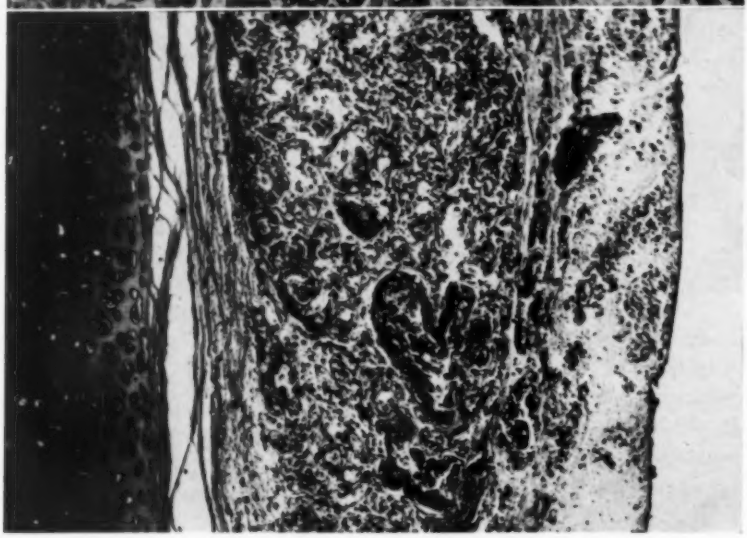

Fig. 3.—Photomicrograph of the lung. Hyperplasia of epithelium, alveolar septal cell proliferation and giant cell formation are present. Intranuclear inclusions are indicated by arrows. (Hematoxylin and eosin; ×250.)

Fig. 4.—Photomicrograph of the trachea. Marked inflammation and metaplasia of the acinar elements of the submucous bronchial glands are present. (Hematoxylin and eosin; ×120.)

DR. TOCH.—At the point when it does occur, the patients are so sick that they may die from other causes.

DR. SIDNEY KIBRICK.—While this child might not have had as adequate an antibody response as a normal child, yet she had been getting blood transfusions. This may have "modified" her measles, as in a patient given gamma globulin. Thus the incubation period may have been prolonged.

Koplik's spots may not be present in modified measles and the absence of any rash may be a manifestation of the partial protection she had received from her transfusions.

DR. CRAIG.—This child, as suspected, had a *typical giant cell pneumonia,* presumably due to infection with measles virus, with marked alteration of the lung parenchyma. The lungs were two to three times enlarged, distended, firm, and nonrepitant. There was marked proliferation of the alveolar septal cells, with many multinucleated giant cells and typical eosinophilic intranuclear and basophilic intracytoplasmic inclusions (Fig. 3). The bronchial glands also were involved with proliferation of the epithelium and squamous metaplasia (Fig. 4). Giant cells were also found in the regional lymph nodes. In no other organ of the body was there evidence of infection with measles virus.

The leukemic process was not marked, there being very little infiltration into the liver (Fig. 5), though the liver was enlarged. The bone marrow was hyperplastic, and, though immature myeloid cells were present, the erythroid series predominated and many megakaryocytes were seen (Fig. 6). I would not consider, from the picture, that her death could be attributed directly to the leukemic process or to chemotherapy. All autopsies in cases of giant cell pneumonia have been performed since 1946. In all of these there has been underlying severe disorder; one case of cystic fibrosis of the pancreas, one of disseminated neuroblastoma, one of Hand-Schüller-Christian disease, 2 of enteritis, and several cases of leukemia. From a number of these, measles virus has been isolated in tissue culture.

DR. ANNA MITUS.—In 1956, Dr. McCarthy and I[5] in Dr. Enders' laboratory, studied 3 cases of giant cell pneumonia, among those mentioned by Dr. Craig, and we were able to isolate an agent which was serologically and cytopathogenically indistinguishable from the virus of measles. None of these children had a history of rash or other characteristic signs of measles, but all had been exposed to measles. One child received gamma globulin just prior to his terminal illness; 2 of the children did not. The terminal illness was characterized by respiratory difficulty. The first 2 patients had very severe progressive bronchopneumonia, resistant to antibiotics, which lasted from one to six weeks. The last patient had a slight cough and died with fulminating severe cyanosis. The virus was isolated in the first case from bronchial secretions, in the second case from the lung, and in the third case from the lung and liver. At autopsy all the children presented the signs of their primary disease and a typical giant cell pneumonia, just described by Dr. Craig.

Five to seven days after inoculation of the tissue cultures, we observed the appearance of typical giant cells, indistinguishable from those produced by the virus of measles, with the formation of intranuclear inclusion

Fig. 5.

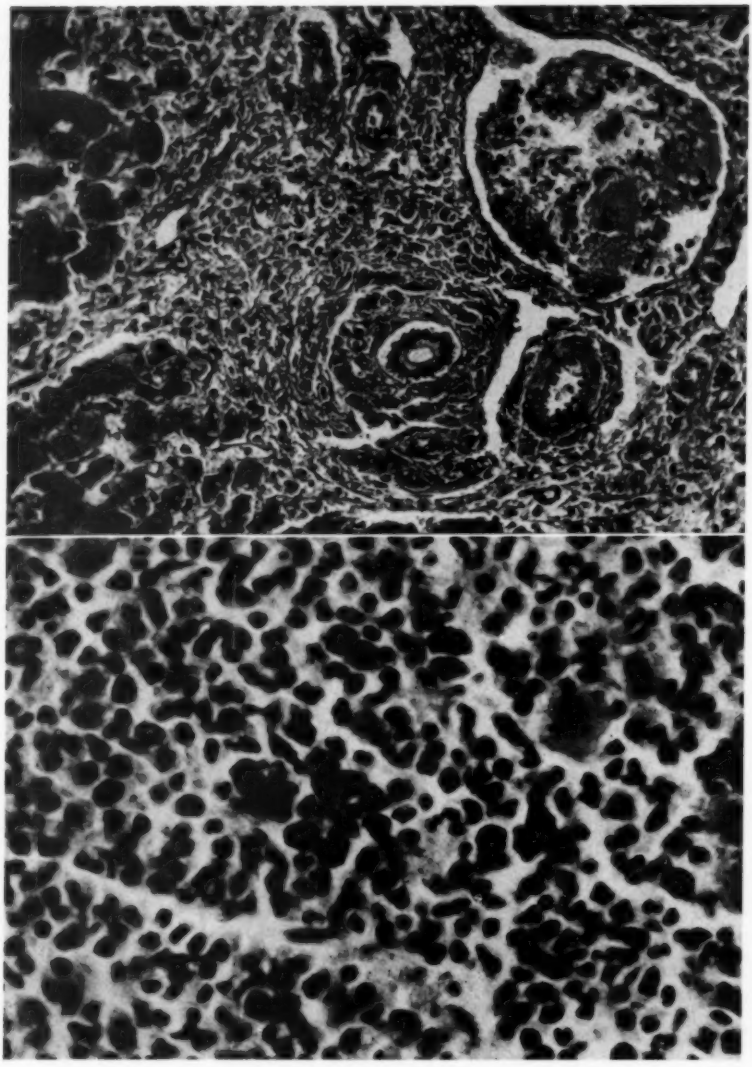

Fig. 6.

Fig. 5.—Photomicrograph of the liver. A few lymphocytes are present in the portal triad. No leukemic infiltrate is present. (Hematoxylin and eosin; ×250.)

Fig. 6.—Photomicrograph of bone marrow. The marrow is hyperplastic, but young myeloid cells predominate; megakaryocytes are present. (Hematoxylin and eosin; ×500.)

bodies. We adapted the virus to amnion, monkey, kidney, and HeLa cells.

We have tested this isolated agent in three monkeys, all of which showed a very significant antibody increase. The agent was isolated again from the blood of one of the monkeys.

The work of Dr. John Adams[6] has suggested that giant cell pneumonia may be caused by the distemper virus. In tests with convalescent serum from dogs with distemper mixed with the measles virus, or of distemper virus mixed with human convalescent measles serum, there was no neutralization in either instance. This indicates that our cases of giant cell pneumonia are not related to distemper virus.

Our experiments indicate then that certain cases of giant cell pneumonia are caused by the virus of measles. The question arises as to why the same agent can cause two conditions that differ so greatly. It is possible that this difference lies in an altered host-virus relationship. In our series, all the children were suffering from chronic debilitating disease which might have altered their response to the virus of measles.

DR. JANEWAY.—I think Dr. Enders has had the feeling that many of the pathological manifestations in some of the exanthematous diseases represent interaction of antigen and antibodies. It seems to me that this is perfectly possible. Dr. Berenberg and I tried to demonstrate this by injecting gamma globulin, which contains quite a lot of measles antibody, into the skin of patients with early cases of measles. We hoped to demonstrate a flare-up of the rash in the area. We obtained very indefinite results.

No one has been lucky enough to make a diagnosis of giant cell pneumonia in a live patient, so blood tests for antibodies could not be made.

DR. KIBRICK.—I noticed that, of the patients in whom there were no skin manifestations, the majority were infants, so there is the possibility of a passive maternal protection modifying their disease. In the older children with this disease, it would be of interest to know whether blood transfusions had been given. Antibody thus supplied may have modified this disease and suppressed the rash.

DR. JANEWAY.—It is interesting that when the children with agammaglobulinemia, who have a marked inability to make antibodies, have an attack of measles, their course is not unusual and they apparently develop an immunity to measles.

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Comments on Current Literature

HEMOLYSIS OF ERYTHROCYTES

THE mechanism by which hemolysis of the erythrocytes is brought about in favism and in certain hemolytic anemias which appear to be dependent upon extrinsic factors is not entirely understood. Recent serologic studies[1] have stressed immunologic aspects in the etiology of favism. By means of in vitro hemagglutination phenomena antibodies to the fava bean were identified in the serum of an untreated patient suffering from favism. The same phenomena could be demonstrated using the serum of rabbits immunized against fava bean extract. Many reports over a period of years have emphasized the importance of individual variation in erythrocyte morphology and the unique capacity of the erythrocyte to respond to foreign substances. It seems logical that basic defects in the patient's erythrocytes might render them susceptible to hemolysis upon exposure to a substance which otherwise would not cause hemolysis. The glutathione instability of drug-sensitive red cells is now well recognized, and tests for the detection of low levels of reduced glutathione (GSH) have been in use for some time. Incubation of such deficient erythrocytes with acetyl phenylhydrazine causes the appearance of abnormal numbers of Heinz bodies in the cells, as well as a marked decline in their reduced glutathione content. This test, known as the glutathione stability test, is a sensitive method for the detection of individuals whose erythrocytes exhibit the defect.[2]

The glutathione of normal human erythrocytes is apparently in a dynamic state, its concentration being dependent upon the rates of its formation and destruction, and also on the capacity of the red cells for maintaining glutathione in the reduced state. Reduced glutathione is an important source of free sulfhydryl groups (–SH) which are functional requirements for a large number of cellular enzymes and coenzymes. The reduction of the oxidized compound (GSSG) is thought by some investigators to be catalyzed by a specific enzyme which has been found in human red cells and in other tissues of the body.[2] In recent years a number of investigative studies has indicated that compounds containing sulfhydryl groups may play an important role in maintaining the integrity of the erythrocyte. Reduced glutathione comprises more than 95 per cent of the reduced nonprotein sulfhydryl compounds in the red cell. Beutler and his associates[2, 3] were among the first to demonstrate that reduced glutathione is diminished in erythrocytes from Negro patients with certain types of drug-induced hemolytic anemia. Subsequently defects in glutathione metabolism were related to a deficiency of glucose-6-phosphate dehydrogenase in the erythrocyte, and recent studies indicate that several metabolic defects may be interrelated in abnormal erythrocyte metabolism, the defective complex thought to be determined genetically—inherited as a sex-linked

or sex-modified trait, or perhaps dependent in inheritance upon a sex-linked gene of variable expression. Whatever the mode of inheritance, the tendency to familial occurrence of this enzymatic deficiency intrinsic in the erythrocytes is definite. The trait occurred in an over-all percentage of 4.6 in a random sample composed of 305 human subjects, and was more than five times as common among healthy American Negroes as among healthy white subjects.[4] Careful inquiry into the family history usually reveals more than one member showing the trait in some degree.

In 1958 Gross, Hurwitz, and Marks[4] reported erythrocyte glucose-6-phosphate dehydrogenase deficiency in certain individuals with a history of hemolytic anemia due to ingestion of naphthalene, chiefly moth balls, to fava bean consumption, or to drugs, or of undetermined cause. These authors made a study of 18 families in each of which at least 2 members showed enzymatic defects of the erythrocytes. In accord with previous investigators, they conclude that alterations in glutathione metabolism are associated with erythrocyte response, and that the deficiency in erythrocyte glucose-6-phosphate dehydrogenase is intrinsic, probably inherited as a sex-linked recessive which may also be sex modified. Except in very young infants an alteration in reduced glutathione stability upon incubation with acetyl phenylhydrazine was associated consistently with a deficiency in glucose-6-phosphate dehydrogenase. Infants under about 60 days of age may show a striking instability in erythrocyte metabolism, despite high levels of glucose-6-phosphate dehydrogenase activity. Transient instability of reduced glutathione in the relatively immature red blood cells of normal newborn infants is well recognized,[2, 4] and was described in detail by Zinkham and Childs[5] in connection with studies of vitamin K and various metabolites of the erythrocytes in the newborn period.

Zinkham and his associates have been interested for a number of years in abnormalities of the erythrocytes in connection with hemolysis in various hypersensitivities including that associated with favism. Detailed studies on 2 patients with favism were reported by Zinkham, Lenhard, and Childs[5] in 1958. One of these patients, a boy of Greek extraction, had been the subject in early childhood of a previous report on favism. His brother also had experienced repeated attacks of icterus. Evidence of intrinsic deficiency in erythrocyte metabolism was noted in both brothers. The father of these boys had an equally prominent deficiency in glucose-6-phosphate dehydrogenase activity; however, he had never suffered from any definite clinical manifestations following ingestion of fava beans, and stated that he had never consumed the raw bean, but only those that had been cooked. In the erythrocytes of the second patient, also of Greek extraction, characteristic abnormalities of glutathione metabolism were demonstrated. The father of this boy also manifested the deficiency as determined by glutathione stability tests. Intermediate values for glutathione stability were obtained in both mothers in these Greek families. Another study by Zinkham and Childs[6] concerns glutathione metabolism in erythrocytes from patients with naphthalene-induced hemolytic anemia. Four patients are reported upon who suffered from hemolytic anemia following exposure to naphthalene; all were Negroes, 3 males, one female. Erythrocyte abnormality in glutathione metabolism was demonstrated in all 4 patients by the determination of glutathione concentration in whole blood and by stability studies. One of these patients was a newborn infant who must have been exposed to naphthalene through the placenta, "since both he and his mother had profound hemolytic anemia, but she alone had ingested moth balls," having had an unnatural craving for the

odor and an unnatural desire to suck on moth balls during her pregnancy. Repeated stability tests carried out on the infant's erythrocytes in the neonatal period and during the first 3 months of life led the authors to the conclusion that, while a certain metabolic instability is characteristic of normal erythrocytes in the newborn period, true deficiencies in glutathione metabolism tend to "express themselves only in older erythrocytes."

At the May, 1959, meeting of the American Pediatric Society, Zinkham and Lenhard[7] reported observations on the "Significance of Primaquine-Sensitive Erythrocytes in Patients With Congenital Nonspherocytic Hemolytic Anemia." They pointed out in this presentation that "the term 'congenital non-spherocytic hemolytic anemia' has been applied to a variety of congenital hemolytic disorders," and that a "review of reported cases indicates that not all patients with this diagnosis are suffering from the same disease." Metabolic defects in the erythrocytes were described in some of these patients. Over a 2-year period Zinkham and Lenhard studied glutathione metabolism and glucose-6-phosphate dehydrogenase activity in the red cells of 6 patients with nonspherocytic hemolytic anemia. These patients were from 4 separate families, one being American Negro, and the others of American Caucasian ancestry—Dutch, French, or English. While all of these patients had developed hyperbilirubinemia in the neonatal period, their subsequent clinical courses had differed. Two of them required frequent transfusions before splenectomy at 2 and 3 years of age. Although hemolysis continued after splenectomy, transfusion requirements were decreased greatly. In these 2 patients the glutathione stability test and assays for red-cell glucose-6-phosphate dehydrogenase gave normal results. In the other 4 patients the degree of anemia was milder, the rate of hemolysis being accelerated on occasion following infection. One of these children had experienced a severe hemolytic episode following the ingestion of phenacetin. In these 4 individuals a markedly abnormal glutathione stability test was obtained and the glucose-6-phosphate dehydrogenase was extremely deficient. Studies carried out on the families of these 4 patients revealed that the defect was present in other members, and in one family could be followed for 3 generations. The authors are of the opinion that glutathione metabolism and glucose-6-phosphate dehydrogenase activity studies will aid in the specific classification of the congenital nonspherocytic hemolytic anemias.

Under certain circumstances clinical hemolysis would seem to result from exposure to toxic substances in those individuals who have a marked deficiency in glucose-6-phosphate dehydrogenase and unstable erythrocyte metabolism. In favism and certain drug-induced hemolytic anemias the mechanism of red-cell damage may be analogous. Further investigations in this important field will be of considerable interest.

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Correspondence

To the Editor:

Scant attention has been given in pediatric literature to the contributions an educator can make to the habilitation of the young handicapped child. At a recent ortho-psychiatric meeting in San Francisco, Jane Phelps, the nursery school teacher in Children's Hospital Cerebral Palsy Program, discussed her observations. The paper was well received by physicians, psychiatrists, and educators alike, and several expressed the hope that it would be given wide distribution. The main points of the discussion are presented her under the headings: The Parents, The Children, and Diagnostic Observations.

THE PARENTS

"The parents require the most careful preparation for the beginning days of nursery school. The profundity of the parents' despair cannot be overestimated, for with most of our parents the diagnosis of a handicap is new. The nursery school is usually the parents' first experience in seeing n group of handicapped children together. Some children will be more handicapped than their own, some less so. The constant support the parents need in having accurate medical information repeated over and over cannot be overemphasized. The parents of a mildly spastic child may erroneously anticipate that their child will grow up to be like a severely athetoid child. Experience has taught us that we must be alert to the unspoken questions and misconceptions that are typical of parents new to the program. Here we are working with parents who are making a variety of attempts to help the child on the one hand and, in many instances, to deny the problem to themselves on the other. They may be waiting for the child 'to grow out' of it, or their expectations may be unrealistic and they may be angry and hostile or depressed and apathetic.

"We have also learned that parents may see attendance in a school situation as implying educability or trainability and such is not always the case. We therefore indicate that the first 6 weeks or so are an evaluation period in which we determine whether or not this nursery school is suitable for this child. It is basic to our discussion of what a preschool program can do for the brain-injured child to stress the fact that in this most critical preschool period one accomplishes with the child only what one is able to accomplish with the parents: helping them to accept the diagnosis and to develop an accurate picture of their child. The preschool period often marks the start of a process in which parents are just beginning to perceive the implications of the diagnosis for their child and the family unit. The birth of a handicapped child into a family is much like dropping a pebble in a pond: the effects are wide and far-reaching and affect the siblings, the grandparents, relatives, and friends of the family.

"From our experience we have learned the need for developing a flexible kind of parent education program. This may include films, speakers at monthly evening meetings, and discussion groups, but it is the direct kind of parent participation in the nursery school that enables the staff to be alert to the distortions and unasked questions that parents reveal in our day-to-day contact with them. It is here that we begin to understand the variety of attempts the parents make to 'negate' the evidence. There is tremendous advantage in being located in a medical setting where both parents and staff have easy access to the pediatrician, the psychiatrists, and the psychologists."

THE CHILDREN

"We have evolved a definite philosophy in relation to these children. We attempt to

provide simple social play directed toward emotional satisfaction in order to release whatever potential the child may have for later learning experiences. Some of the more basic satisfactions may have been restricted at home. Thumb sucking, chewing toys, feeling or smelling toys, and seemingly random, purposeless activity is not restricted unless harmful to the child or to others. It is obvious that these handicapped children are both immature and inexperienced to a greater degree than the nonhandicapped child of the same age. We share a deep concern with other disciplines as to the factors which contribute to the formation of the child's self image. It is our feeling that these children need tangible physical evidence of affection and acceptance. They need to be picked up and comforted, and picked up and played with, with expressions of acceptance verbalized when appropriate and when spontaneous. It is all too common an experience that these young children have already been exposed to reactions of revulsion, disgust, and curiosity. In the preschool years, quite apart from whatever else we can offer, if we can help them form an image of themselves as being loved, wanted, and worthy of respect, we will have contributed something basic to their development. If the basic experience here is good, we will have given them the strength to meet the stress of future contacts which may be less good.

"In this area we are reminded of various comments mothers have made to us: 'If he just didn't embarrass me by smelling everything, I could stand it better.' 'If only he didn't drool so much, I wouldn't mind taking him out.' Or, 'When my other children were 4 years old and went through a silly stage, it wasn't so bad. But when Billy does it, I'm afraid people will think he's not right in the head.'

"Because parents are already so puzzled by the odd extremes of behavior they have struggled with, they may have handled it by pressuring the child 'to stop it.' If the child's behavior is characteristically 'spotty' and swings from behavior quite appropriate to his age to behavior that seems a reversion to earlier infantile patterns, he may have had his personal dignity assaulted by 'don'ts' far more than a normal child might have to bear.

"We remember that these children may have been under medical, surgical, or psychological care for long periods of time, and may not have had much time to be what they are—young children. Whatever their chronological age, they must not be pushed into patterns of conformity beyond their maturational skills. In nursery school they are not forced to sit during snack period for longer than they are able, or forced to sit and listen to music when they should be playing.

"During the morning session the activities are much like those one would see in any nursery school although it is quieter, since many of the children do not talk; there is less moving around, since many of the children are not ambulatory, and the pace is quieter and somewhat slower. It is important that a room be available where the more typically brain-damaged child may go in order to recover his equilibrium. Such children are often conspicuous in a group, and, when pressures (which the adult cannot always see) have become intolerable, the child can be observed standing in the middle of the room with his hands over his ears, or seeking the haven of the adult's lap, or, more typically, bursting into tears. These children need a program that is individually designed for them; it will vary from day to day."

DIAGNOSTIC OBSERVATION

"During the period of unrestricted play and those periods in which some structuring is necessary, the teacher can be alert to observing the behavior, verbal responses, and problem-solving methods that offer clues as to the nature of the child's more subtle disabilities. Some of these children react to stressful situations with an increase in drooling, with unusual motor behavior such as toe walking, and an increase in awkwardness in fine finger coordination.

"One of the essential contributions a program such as ours can offer is to accumulate observed data that tends either to confirm the diagnosis or offer new insight as to the real nature of the child's problems.

"The kind of observation we can make in the playroom is a long-term process and great care should be taken to avoid placing

a label on the child that long-term observation does not confirm. We can observe the child struggling because of his inability to organize stimuli into a meaningful whole, and we can observe that he seems to interpret stimuli differently than other children. Over a long period of time we can also watch the development of avoidance techniques which these children utilize to cover up their deficiencies from the simple and direct 'I don't want to do that puzzle' to the more sophisticated 'I'm not feeling well right now.' One can watch these children struggle to remove pieces from a puzzle, expending energy in trying to remove a part that is merely a design painted on the border. The child can be observed trying to work a puzzle, but able to guide the pieces in only by placing his finger in such a way that he feels where the indentations are. We have watched such children during informal story periods, where large, colored pictures are used, and they respond in such a way that we know they are aware only of a small fragment of the total picture, or are concerned with a minor flaw in the paper which is not readily seen by the adult. Some of the children can identify the parts of the body on themselves or in a book but cannot do it on the doll. There is about these children a specific quality that suggests *interference* rather than *lack*. One must try to separate to what degree the child's anxieties and feelings of inadequacy and helplessness contribute to the formation of this symptom complex. The teacher must try to be alert to the child's changing performance to know whether his failures at present are because he has not yet developed skill in that area but is capable of so doing, or whether it may be an area which is not capable of being developed.

"Therefore, it can be said that the basic contribution a preschool program can make to the brain-injured child is to provide him with as much support and emotional security as we can to help him go on to the next learning situation. The potential of these children is often high, but, without real understanding of their basic pathology, they can be mismanaged. Then, there is superimposed a psychological problem which may make future evaluations almost impossible.

"If the first 5 to 7 years are important for the normal child, they are infinitely more important for the brain-damaged one."

JANE K. PHELPS, B.A.
H. E. THELANDER, M.D.
San Francisco, Calif.

To the Editor:

There is little doubt that early diagnosis of esophageal atresia is becoming more common. The symptom complex of excessive salivation and prompt regurgitation of feedings is becoming well known and usually leads to immediate investigation. Despite this there are still two common "pitfalls" which cause unwarranted delay in diagnosis and these are seen so frequently that it is felt that they should receive further comment.

It is well known that any baby with the symptom complex mentioned above should have a tube passed into the stomach without delay to confirm or exclude esophageal atresia. What is not well known is the ease with which many rubber or plastic gavage tubes can curl up in the upper, blind esophageal pouch and give a false impression of having passed readily into the stomach. We have seen this error made many times, and it invariably delays recognition and treatment by several hours. One can avoid the error by filling the tube with a little contrast medium and then passing it into the stomach under fluoroscopic control. If a blind esophageal pouch is present, a small amount of dye can be injected into it and subsequently removed after x-rays are taken.

The other common cause in delay in diagnosis is confusion between the symptoms of atresia and those of respiratory distress following a difficult labor. We have been told several times that the doctor attending the baby at birth did not suspect esophageal atresia when the baby had "choking spells" because the labor was difficult and possibly associated with hydramnios. The latter should always raise the question of gastrointestinal obstruction in the infant, and excessive salivation in any

newborn infant demands immediate investigation despite the difficulties encountered during labor.

We have recently had a case in which both these diagnostic errors contributed to delay in eventual diagnosis. It would seem, therefore, that further mention of them would not be out of place.

P. G. Ashmore, M.D.
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Correspondence

To the Editor:

As a regular reader of the JOURNAL, a particular advertisement has been of some concern to me. It appears on page 79 of the June, 1959, issue. An asthenic, taut little boy is shown next to a picture of his report card marked by a teacher, indicating her "diagnosis" of anxiety. A tranquilizer is suggested for this problem. The advertisement says, in effect, to dampen all of this boy's responses to difficult problems so that he will be like other children.

Is this what we really want to achieve? The very foundation of personality development is the grappling with and the finding of a solution to these anxiety-producing situations. By use of such ataractics, are we not merely postponing, or worse, replacing this necessary agony of growing up?

The tranquilizers have been of inestimable value in medicine, and specifically in pediatrics in cases of a severe nature, but they are being used all too often to "cool off" a child in a temporary struggle with his problems. Let us not add the adolescent character disorder to our growing list of iatrogenic ailments.

EDWIN A. SUMPTER, M.D.
Nashville, Tennessee

Books

Cerebral Palsy. A Clinical Study of 370 Cases. Marit Skatvedt, M.D., Stockholm, Sweden, July 1948, Monograph Supplement to Acta Paediatrica, Vol. 46, Almqvist & Wiksells International Booksellers.

"Cerebral Palsy is a clinical syndrome consisting of a number of different forms of motor disorder due to cerebral lesions and is characterized by lack of control and coordination of the voluntary muscles." From this definition Dr. Skatvedt reviews the history of cerebral palsy from Dr. Little in 1853 to Dr. Perlstein in 1954. He has analyzed the distribution of his patients into clinical types and studied the various etiological factors. Hereditary genetic factors are rare.

He reviews the diagnostic criteria and considers in considerable detail pneumoencephalographic studies, which are less frequently done in the United States today. There is a discussion of the mentality, speech abilities, incidence of convulsions, and of other abnormalities.

Treatment is mentioned only briefly, and there are no data as to results of treatment.

Dr. Skatvedt has given a very good monograph on etiology and diagnosis of cerebral palsy with statistical reports on 370 cases.

Differentialdiagnose neurologischer Krankheitsbilder. G. Bodechtel, Stuttgart, 1958, Georg Thieme Verlag, 975 pages.

This is an extremely well-organized and well-documented reference book concerned with neurological differential diagnosis. The contents have been divided according to both anatomic and pathologic considerations. Such a classification is extremely simple and useful.

The numerous illustrations are superb and certainly complement a splendid text. The section devoted to cerebral circulation, which includes arteriographic studies, is especially well done and is illustrated by arteriograms.

This text should be translated into English and made available to more persons in clinical neurology.

W. S. F.

Current Problems in Allergy and Immunology. William Kaufman, Editor, Basel and New York, 1959, S. Karger, 988 pages. Price $14.40, sFr. 60.

This volume contains some sixty articles which were published initially in several issues of the *International Archives of Allergy and Applied Immunology* as a Festschrift to Béla Schick on the occasion of his eightieth birthday. The assemblage of these papers into a single volume will be meaningful to the allergist and immunologist. Of a different order of importance is the honor paid to one of pediatrics' truly great men. Schick's contributions, especially in the fields of allergy and immunology, insure him a niche in medicine's Hall of Fame; his stature in the pediatric world today is based perhaps as much on the affection and admiration of the many who have been privileged to know him and who see in him an ideal practitioner, teacher, and investigator.

Editor's Column

"POOR PROTOPLASM"

"POOR protoplasm" is an expression which has become firmly established as part of the argot of pediatric house officers and is frequently heard in other medical circles. A brief survey of the *aficionados* of the term reveals that this is an appellation applied to patients with obscure or ill-defined disorders in whom manifestations such as failure to thrive, disturbance of growth, mental retardation, and repeated infection are common. These findings may or may not occur in association with apparent congenital malformations. The label is generally applied only after the usual laboratory studies have failed to offer a diagnostic lead. It implies something odd or unfamiliar; in essence it is simply another way of saying we do not know the cause for the patient's disorder. Too often, however, "poor protoplasm" is stated with a finality that precludes any further deliberation of the problem. It connotes a sense of hopelessness and abandonment of any prospect of discovering the basic disorder.

Since protoplasm is the essential material of all cells and is composed of proteins, carbohydrates, lipids, and inorganic salts, etc., it is evident that patients with "poor protoplasm" must of necessity have a disorder of one or more of its component parts. The well-defined disorders of these components comprise the majority of the entities known as the inborn errors of metabolism (Garrod) or the molecular diseases (Pauling). Thus, it follows that many patients with inborn errors of metabolism have in a sense "poor protoplasm" or, more accurately, "inferior" or "defective" protoplasm. The converse of this proposition is probably also true, i.e., patients with defective protoplasm very often have an inborn error of metabolism.

A boy who had nineteen episodes of sepsis in a four-year period might easily have qualified for the "poor protoplasm" fraternity before 1952. But in that year Bruton discovered that such a child had defective synthesis of gamma globulin and a rational therapeutic approach was thus evolved. Today a patient with this clinical history presents no diagnostic or therapeutic challenge and no one would refer to him as exhibiting an example of "poor protoplasm." An eczematous, mentally retarded child who has frequent seizures certainly had the essential for the "poor protoplasm" designation before 1934. It was in this year that Fölling described phenylpyruvic oligophrenia, a disorder which has

been intensively investigated and for which an effective dietary therapeutic regimen has evolved within only twenty years. It is interesting that it was the "mousy" odor of the urine that was the impetus to the investigation of this disorder just as the odor of maple syrup from the urine of four siblings with cerebral damage led Menkes to the characterization of maple sugar urine disease.

One can give many examples of this transition from the vague "poor protoplasm" to the well-characterized inborn error of metabolism. But we must not ignore some of the other pathogenetic mechanisms which have been found to cause "poor protoplasm," such as nutritional deficiency (pyridoxine deficiency seizures), autoimmunization (hypothyroidism), and iatrogenic factors (retrolental fibroplasia). The recent demonstration of chromosomal aberrations in patients with gonadal dysgenesis, Klinefelter's syndrome, and mongolism marks the beginning of an exciting new era in the elucidation of another group of patients with "defective protoplasm."

"Poor protoplasm" is a wonderfully droll label with a modicum of accuracy as it is generally applied in medicine today. However, the connotations that it carries are such that there is little excuse for its continued usage. Much can be learned about these interesting but enigmatic patients depending upon the facilities and knowledge available, the perceptiveness and imagination of the physician, and the diligence with which they are studied. Let us not casually dismiss our difficult cases with a shrug of the shoulder and a vapid "poor protoplasm."

ANGELO M. DIGEORGE